

BULLETIN

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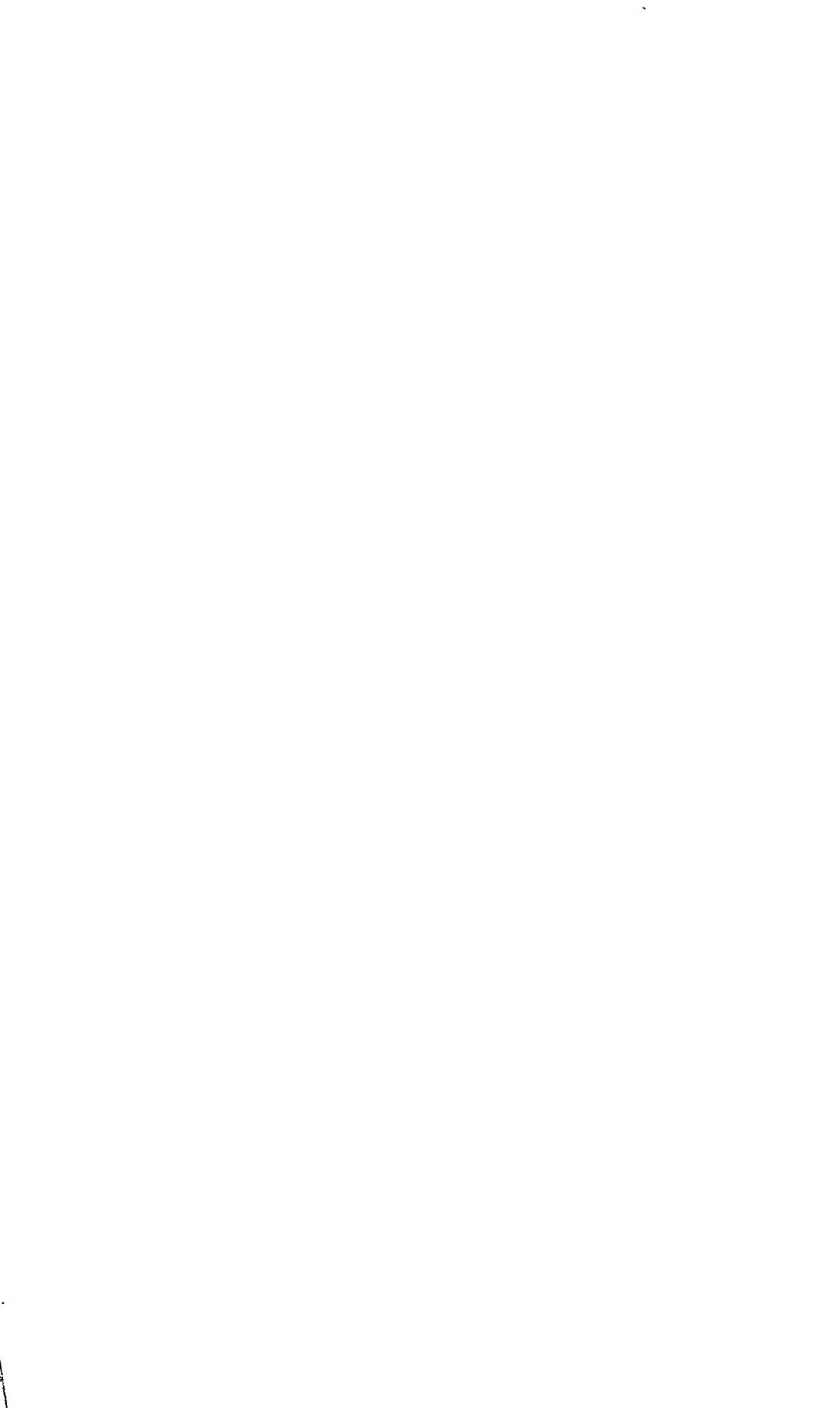
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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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JANUARY 1948

RECENT ADVANCES IN TREATMENT
OF LYMPHOMAS, LEUKEMIAS AND
ALLIED DISORDERS

*The Bulkley Lecture**

LLOYD F. CRAVER

Physician, The Memorial Hospital

No one can feel satisfied about the treatment of cancer today. While notable progress has been made in the attack on cancer by surgery, x-rays and radium, obviously these agents can succeed in curing the disease only when they can completely remove or destroy all of it, and even if successful may leave the patient badly mutilated. Hence the constant efforts to learn the forces controlling normal and abnormal growth, reflected now in this country by the organization of the Committee on Growth of the Division of Medical Sciences of the National Research Council. The Committee on Growth quite properly has panels on widely diversified branches of knowledge pertaining to growth, such as enzymes, protein chemistry, botany and genetics. Naturally one important aspect of the investigations of factors influencing abnormal growth is a study of the possibility that various agents introduced into the body as a whole may selectively affect neoplastic cells

* Given 28 March 1947, Friday Afternoon Lectures, The New York Academy of Medicine.

and kill such abnormal cells without seriously impairing the patient's health by excessively affecting normal cells.

Such was Ehrlich's hope for a *therapia sterilans magna* for syphilis. While his hope for syphilis was not realized, his discovery of salvarsan and neosalvarsan represented enormous strides forward in the treatment of that disease. Similarly, with cancer, it is unlikely that any single agent will be found that can be a sterilizing agent, but there is reason to hope that significant progress is possible towards finding selective therapeutic materials that will kill the disease without permanently damaging the patient's health. The sulfonamides, penicillin, and streptomycin have had sufficient success in infections to add greatly to our respect for the possibilities of chemotherapy.

In the investigative work on these problems of learning the causes of, and seeking effective constitutional agents against cancer, the group of neoplastic diseases comprising the lymphomas and leukemias has come into great prominence. Both in animals and in humans these processes are available in abundance, and readily provide measurable features, (biopsies, size of lymph nodes, spleen and liver, basal metabolic rate, blood counts, marrow studies) which enable ready determination of therapeutic effects.

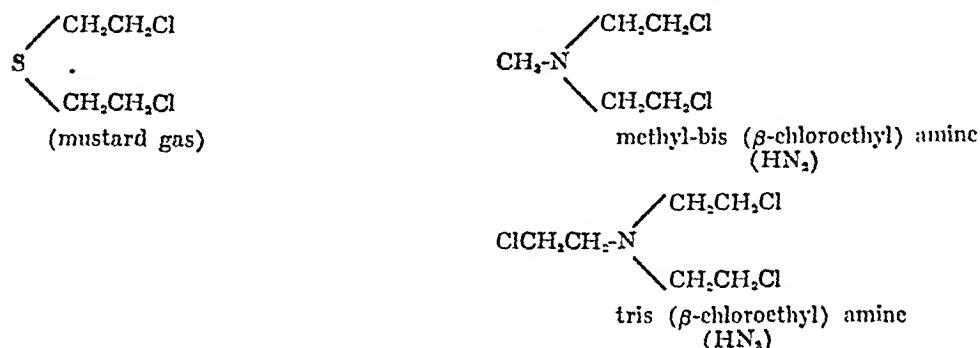
The past decade has witnessed important progress in efforts to control lymphomas and leukemias. These relatively recent advances may be broadly divided into two main categories: 1) chemotherapeutic and 2) radiotherapeutic. In part, the radiotherapeutic category merges with the chemotherapeutic one, in the sense that the selective absorption of the radioactive isotope of phosphorus depends on the metabolic need of cells for phosphorus.

In chemotherapy the agents by means of which recent advances have been made are 1) the nitrogen mustards, 2) urethane and 3) stilbamidine. The older agents, such as arsenic and benzol, have contributed no recent advances, with the possible exception of the report of susceptibility of Furth's chloroleukemia, 1394, of mice to benzene.¹ In the past several years trials of aminopyrine, colchicine and thiouracil² in the treatment of leukemia have been disappointing. The workers who treat lymphatic leukemia with extracts of urine or feces from patients having myeloid leukemia, and vice versa, on the intriguing postulation of lymphokentric and myelokentric acid, report partial remissions.³

In this paper, therefore, the discussion of chemotherapy will be directed mainly towards the nitrogen mustards, since they currently are in the limelight, and some mention will be made of urethane and stilbamidine, since they too have very recently come to notice.

THE NITROGEN MUSTARDS

These are nitrogenous analogues of mustard gas, bis(β -chloroethyl) sulfide, as shown by the following structural formulae:



Following World War I a few reports concerning mustard gas described systemic effects on hematopoietic tissues, gastrointestinal tract, and electrolyte and fluid balance, as well as on the growth of experimental tumors, but in general, between the two wars, very little research was done on chemical warfare agents. Early in World War II the possibility that such agents might be employed caused a resumption of research on their biological effects, and as the nitrogenous analogues of mustard gas were believed to be candidate warfare agents they were produced in quantity and studied intensively. It was soon learned that not only were they powerful vesicants on contact with tissue, but that their absorption systemically resulted in toxic action on various tissues, generally proportionate to the degree of cellular proliferation. Thus the most marked pathological changes are seen in the lymphoid tissues of the thymus, lymph nodes, and spleen, in the bone marrow, and in the intestinal mucosa. Lymphoid tissue throughout the body is rapidly affected, showing disintegration of lymphocytes within 5 to 10 hours,⁴ resulting in marked shrinkage in volume of lymphatic tissue. All elements of the hematopoietic system are affected. Lymphopenia is followed by neutropenia, and there may be thrombocytopenia and anemia. Large doses may cause almost complete aplasia of the marrow.

Studies of the nature of the effects of nitrogen mustards on cells

reveal no similarity to the effects of any other chemical agent, but many similarities to the effects of x-rays.⁵

These observations led to the suggestion that these agents might be useful in controlling certain neoplastic processes, particularly those of the lymphoid system.

Since the nitrogen mustards were potential chemical warfare agents the matter of arranging for clinical study of their effects was a governmental function. By coöperation between the Army's Chemical Warfare Service (CWS), the National Defense Research Committee (NDRC), the Committee on Medical Research (CMR), of the Office of Scientific Research and Development (OSRD) of the National Research Council (NRC), and with aid from the Jane Coffins Childs Memorial Fund for Medical Research, the clinical investigative program was formulated, and studies were begun under contract between the OSRD and Yale University.

Accordingly in 1942 and 1943 Gilman, L. S. Goodman, Lindskog and Dougherty at the New Haven Hospital treated a series of 7 patients in far advanced stages of cancer by intravenous injections of *tris* (β -chloroethyl) amine hydrochloride.

The first patient selected, in late 1942 for trial of the *tris* compound (HN_3) was one who had advanced radioresistant lymphosarcoma. He was treated by Lindskog at Yale.⁶ The dose chosen, 10 consecutive daily doses of 0.1 mgm of *tris* (β -chloroethyl) amine, based on results in experimental lymphosarcoma in mice, was too large, but produced rapid regression and symptomatic improvement. However in one month the patient's tumor masses recurred. Two additional courses of injections were given, but were productive of only slight temporary benefit, and the patient developed a leukopenia of 200 white cells and a thrombocytopenia of 22,000 platelets, and accompanying slight fever, gingivitis, periodontitis and cutaneous purpura. Death appeared to have been hastened by these effects on the marrow.

Thus, while it was obvious that the drug was so toxic to the marrow that it produced dangerous effects in large doses, the striking regression of large radioresistant masses of lymphosarcoma encouraged further clinical trials, particularly in the lymphomas and leukemias.

The result in this case, and the rapid regression in another case of lymphosarcoma were reported in a restricted communication by Gilman, Goodman, Lindskog and Dougherty, dealing with the first clin-

cal trials of nitrogen mustards on a group of six patients in the terminal stages of various neoplastic diseases.⁵

Soon afterward, at the Billings Hospital in Chicago, Jacobson and his group⁷ began the study of the effects of methyl-*bis* (β -chloroethyl) amine on various neoplastic diseases of the lymphatics and blood-forming organs. They were the first to use nitrogen mustard on Hodgkin's disease.

Another group working at the University of Utah (L. S. Goodman and Wintrobe) began work on nitrogen mustards in 1943 and recently published⁶ a report on their thirty-four cases, together with 16 treated by Dameshek in Boston, ten treated by M. J. Goodman in Portland, and seven treated by L. S. Goodman and Gilman at New Haven.

In October 1944 by authorization of the Chemical Warfare Service and the National Research Council, Memorial Hospital undertook a study of the clinical effects of methyl *bis* (β -chloroethyl) amine. At the request of Dr. C. P. Rhoads a brief survey of the cases of Hodgkin's disease that Jacobson and his group had treated at the Billings Hospital was made by J. C. Abels and the writer, and convinced us that this compound had something to offer in the palliation of Hodgkin's disease in relief of constitutional symptoms, and in resolution of nodal masses and pulmonary infiltrates, although lesions in the bones did not seem to have responded well. We returned to begin this work with the feeling that while the HN₂ compound could produce remissions of Hodgkin's disease, we wanted to find out if it were any better than x-ray treatment, and in particular whether it could prove to be a reliable resource for those cases that had become refractory to x-ray treatment either by reason of marked generalization or because of genuine radio-resistance. Therefore our earlier selections were cases that seemed unsuitable for x-ray treatment, and our early results were rather disappointing. However, as further trials were made it appeared that this chemotherapeutic agent offered another tool for the palliation of Hodgkin's disease and other lymphomatous processes and the leukemias, and the fact that there were many related compounds still to be investigated made it obviously worth while to continue the work.

A most helpful impetus was given to our work when through the initiative of C. P. Rhoads we obtained the assistance of Captain David Karnofsky from Edgewood Arsenal, as he was familiar with the secret prior animal and other investigative work that had been the subject

of restricted reports.

The first open announcement of the work that had been done on the evaluation of the nitrogen mustards was made by Gilman and Philips of the Pharmacology Section of the Medical Division of the Chemical Warfare Service in Science in April, 1946.⁵

In June 1946 C. P. Rhoads⁸ as Chairman of the Committee on Growth of the National Research Council published in the Journal of the American Medical Association an official statement summarizing the therapeutic status of the nitrogen mustards up to that time and announcing the availability of methyl-*bis* (β -chloroethyl) amine hydrochloride for free distribution to qualified institutions for experimental purposes, through the Committee on Growth in coöperation with the Chemical Warfare Service. Since then the material has had fairly wide trial by a good number of investigators in different parts of the country. By far the experience with nitrogen mustards has been mostly with HN₂ (the methyl-*bis* compound).⁹ Since there are, as stated by Gilman, literally hundreds of congeners that remain to be synthesized, screened for possible therapeutic, rather than toxic chemical warfare use, and tested, it is evident that the work has barely begun, and it is distinctly possible that far more useful compounds may come to light.

Now, at Memorial Hospital, we have two programs going on side by side. First is the continued further trial of HN₂ and HN₃ on lymphomas and leukemias. HN₂ has come into practically routine trial especially for Hodgkin's disease when the patient has constitutional symptoms resulting from Hodgkin's disease so generalized or if less generalized so much previously treated by x-rays that one hesitates to employ x-ray therapy again. Second, through the Chemotherapy Planning Board of the Sloan-Kettering Institute, as other nitrogen mustard compounds are selected after a screening process, they are tested first on a carefully chosen pilot case in the research ward, and then tried on six cases each of Hodgkin's disease, lymphosarcoma, myeloid leukemia and lymphatic leukemia, either in the research ward or on the regular medical service.

It is too early to report here the results from the newer nitrogen mustard compounds, and therefore this report will deal with cases of lymphomas and leukemias that have been treated by either HN₂ or HN₃. Most of the patients were treated by HN₂.

Dosage and Method of Administration. Methyl *bis* (β -chloroethyl)

amine hydrochloride, a white crystalline powder, is now available packaged, in 20 cc. rubber capped vials, each containing 10 mgm. of the dry powder. Immediately before the material is to be used, 10 cc. of physiological saline solution is injected into the vial, and the vial is shaken to bring the powder into a solution containing 1 mgm. in each cc. The desired dose for one injection, usually 0.1 mgm. per kg. of body weight, is then withdrawn into the syringe, and the remainder of the solution in the vial is discarded. It is recommended that the intravenous injection be made within 5 minutes following the preparation of the solution, to avoid loss of potency because of rapid hydrolysis.

The groups in Chicago and Salt Lake City have routinely adopted the plan of rapidly injecting the nitrogen mustard solution into the rubber tubing of an infusion set through which is running freely and rapidly a small infusion of glucose or saline solution. Their reason for this procedure is to avoid chemical thrombophlebitis. Great care must be taken to avoid letting any of the nitrogen mustard escape into the subcutaneous tissue, but we have found the syringe method satisfactory. The injection need not be made slowly, and it seems to make little difference at what time of day it is given.

The usual dose is 0.1 mgm. per kg. of body weight once a day for four to six consecutive days. At first in some of the more seriously ill patients the individual dose was reduced to 0.05 mgm. per kg. of body weight, but when later we found that patients usually tolerated 0.2 mgm. per kg. it no longer seemed necessary to cut the usual dose in half.

Toxic effects. Escape of even a small amount of nitrogen mustard solution into the subcutaneous tissue will cause local pain, followed by swelling, induration and redness. The resultant thickening of subcutaneous tissue may persist for many weeks. Not infrequently a small thrombus forms at the site of injection, but usually this effect is due to poor technique in the case of HN₂. With HN₃ we encountered some marked thromboses, but they have not produced any serious consequences.

Nausea occurs in most patients in from 1 to several hours following the injection, and about half will have retching and vomiting. These symptoms may last from a few to several hours, but almost invariably by the next day the patient is ready to accept another injection. Pyridoxine 100 mgm. intravenously or intramuscularly administered prefer-

ably one-half hour following the dose of nitrogen mustard, rather than before (since pyridoxine is one of the substances mentioned by Gilman as subject to alteration by nitrogen mustard), may seem to allay the nausea and vomiting. We have not routinely used sedation. Severe vomiting may of course be hazardous in a patient with a hemorrhagic tendency, as in acute leukemia or acute lymphosarcoma. One patient with acute leukemia died, apparently of intracranial hemorrhage, following vomiting after an initial injection of HN₂, and a young man with aggressive lymphosarcoma and purpura developed a remarkable purpura of his whole face following a bout of vomiting after an injection of nitrogen mustard.

Naturally with nausea and vomiting occurring daily for four to six or seven days the patients usually lose weight and may become more or less dehydrated. In many instances, however, following the course of injections, along with the lysis of fever, and relief from toxic symptoms of the disease, the patients develop an unusually strong appetite and rapidly regain weight.

Toxic effects on the hematopoietic system are regularly seen following adequate nitrogen mustard therapy. The white cell count may begin to drop before the course of injections is completed. Often a lymphopenia develops in a few days, and is followed by a granulocytopenia, so that some time within 3 weeks there occurs a more or less marked leukopenia. With larger doses or repeated courses, the white cell count may go down to 1,000, or 500 cells or even lower. No one seems to have observed ulcers or other manifestation of agranulocytosis, strangely enough, in these cases, nevertheless when the white count falls to 1000 or less we usually give penicillin prophylactically. We regard the depression of the white cell count as a measure of the adequacy of therapy.

Presumably because of the longer life of the red cell, anemia usually does not become as evident a sign of the toxic action of the drug as does the leukopenia, and sometimes onset of red cell regeneration is shown by an increase in reticulocyte count when there has been only a mild drop in the red cell count. Some patients having a severe toxic reaction to nitrogen mustard may show a rapid drop in hemoglobin. While we have not noted clinical evidence of a hemolytic reaction, Jacobson's group found in selected cases a significant increase in total urobilinogen excretion.

The blood platelets may fall very low in some cases and marked thrombocytopenia may be associated with more or less purpura. On the other hand purpura and petechiae may occasionally be seen in patients whose platelet count is not markedly depressed. In at least two instances in which severe generalized purpura occurred, recovery from this state was followed by a marked and prolonged remission of the lymphomatous process.

In patients in whom anemia, leukopenia, thrombocytopenia and purpura may reasonably be regarded as caused by the disease rather than by previous treatment with some form of radiation therapy or with nitrogen mustard, it may be justifiable to proceed cautiously with nitrogen mustard therapy on the chance that improvement may result. The minimum necessary hematological guide to treatment is a total white cell count daily, and a hemoglobin determination every other day during the period of treatment and at frequent intervals for the next three or four weeks.

No fixed rule can be laid down as to how much nitrogen mustard should be given in one course, or how soon another course should be given. The wide vagaries of lymphomatous and leukemic processes prevent predetermination of exact dosage. Usually the standard course of 4 injections of 0.1 mgm. per kg. of body weight, as recommended by the Committee on Growth to those physicians without previous experience with the drug, is within safe limits, but often in our experience, is insufficient to secure a satisfactory degree or duration of remission. In many cases risk of toxic complications must be assumed if one is to obtain a worthwhile remission. The statement, moreover, that "— immediate systemic reactions would appear to be less severe after chemotherapy with the β -chloroethyl amines than after irradiation —" does not accord with the experience at Memorial Hospital, with the possible exception of those cases that as far as x-ray treatment is concerned would need extensive treatment over the abdomen.

Cases treated. From October, 1944 to March 1, 1947, 114 cases have been treated. Of these, ninety-three cases belong in the lymphoma-leukemia category, and include forty-three cases of Hodgkin's disease, twenty-seven of lymphosarcoma, fourteen of lymphatic leukemia, six of myelogenous leukemia and three of mycosis fungoides.

Results. In diseases so variable as the lymphomas and leukemias and in which a new form of therapy is tested on patients in all stages of the

disease, no statistical analysis is valid on such a relatively small number of cases. However, close observation by those familiar with the behavior of these diseases untreated, or treated by irradiation, does permit at this time confirmation of the few published reports that nitrogen mustards undoubtedly have a beneficial effect on these types of neoplastic disease, and justifies the prediction that chemotherapy with these or related compounds will play an increasingly important role in the treatment of lymphomas and leukemias in the coming years.

Hodgkin's disease. Forty-three patients have been treated for Hodgkin's disease. Our early results were disappointing because we deliberately chose at first mostly cases that had reached the point of failure with x-ray treatment. Some were so far advanced, with hard resistant fibrous bulky masses of nodes that it would well have been like a miracle if any agent caused remission. Then when we began to choose cases that would have been more favorable for x-ray treatment results began to appear. Then the question naturally arose whether nitrogen mustard therapy is superior to x-ray therapy, whether remissions would be as nearly complete or as long in duration as with x-ray therapy, and whether the toxic effects were less or more severe.

On the basis of our experience we distinctly do not recommend nitrogen mustard as the treatment of choice for either the early localized case of Hodgkin's disease, or for the case with beginning generalization in which the disease is still rather regionally localized and in which there are as yet no marked constitutional symptoms. Such cases as a rule will be much better cared for by proper x-ray therapy, with much more likelihood of a good result lasting for a good period, and with less toxic reaction to the treatment.

It is with the cases of more or less generalized Hodgkin's disease, having constitutional symptoms, such as fever, sweating, and itching, that the question arises whether they may best be treated by nitrogen mustard or by x-rays. It seems clear that in perhaps the majority of such cases, if the patient is in good condition, has no evidence of extensive marrow infiltration, and has a fairly good hemoglobin and a normal or elevated white cell count, he may obtain a remission within a week or ten days by means of nitrogen mustard injections, whereas to obtain a result with x-ray treatment might require about 3 or 4 weeks of irradiation daily or every other day. If the patient lives at some distance from the hospital it would be preferable in this type of case for

him to be hospitalized for either type of treatment. While most of our nitrogen mustard patients have been hospitalized it has been found practicable to treat some as out-patients, who live near enough so that they can reach home before the nausea and vomiting begin. One gains the impression also, in this type of case that the after effects in terms of hematopoietic depression may be less prolonged after a course of nitrogen mustard than after a therapeutically equivalent course of x-ray therapy. Unfortunately our impression is that the remissions that follow use of nitrogen mustards in this type of case tend to be considerably shorter. This matter of shorter remission is difficult to assay, and certainly in some cases we have seen fully as good a result if not better than might have been expected from x-ray treatment. These results consist usually of partial reduction of nodes, in the deep as well as the superficial chains, partial clearing of pulmonary deposits, some shrinkage of enlarged livers and spleens, and a fairly rapid disappearance of fever, sweating and other signs of toxicity. Itching and bone lesions have not responded particularly well.

The more aggressive the course of the Hodgkin's disease the briefer have been the remissions following nitrogen mustard treatment.

In the far advanced cases, with very bulky granulomatous masses or with anemia, cachexia and hypoproteinemia, nitrogen mustard seldom does more than produce a slight and brief remission.

Lymphosarcoma. Twenty-seven patients have been treated for lymphosarcoma. The aggressive acute lymphosarcomas do not respond well as a whole, either to nitrogen mustard or x-ray therapy. Either agent may produce some temporary palliation and shrinkage of tumor masses or nodules, but such effects mean little in the general rapid progression of the disease. They may be treated with repeated or heavy courses of nitrogen mustard to the point of severe leukopenia, thrombocytopenia, purpura, and anemia, yet the disease shows little response and progresses rapidly to a fatal termination.

In less aggressive generalized types of lymphosarcoma the palliation may be somewhat better, and in some cases, if dosage is pushed far enough, a remission of a few to several months may be obtained, comparable to that seen in Hodgkin's disease.

In a few cases of so-called lympholeukosarcoma (lymphosarcoma with a leukemic blood picture) remissions of several months have been obtained.

In follicular lymphoma results have so far been rather mediocre. It would seem advisable however to have more experience with this type of case. Its usual sensitivity to x-ray therapy would suggest that by and large these cases should respond well to nitrogen mustard, if the biological action of this chemical is similar to that of x-rays. A probable explanation for the mediocre results in some cases as diagnosed by biopsy is the same as the explanation for the failure of some such cases to respond as well as expected to x-ray therapy; that is, that the biopsy is misleading, in that much of the process has gone on to full blown reticulum cell sarcoma.

Lymphatic leukemia. Fourteen patients with lymphatic leukemia have been treated. In some chronic cases the white cell count has fallen and there has been some reduction in the size and consistence of the enlarged liver, spleen and nodes, but usually the differential white cell count, when there have been 90 to 100 per cent lymphocytes, is not changed, and there is seldom evidence of red cell regeneration.

Myelogenous leukemia. Six patients with myelogenous leukemia have been treated. Remissions may result but do not last more than a month or two.

The acute leukemias have in our experience shown an unsatisfactory response to the methyl *bis* or the *tris* compounds. One of the other congeners seems to offer more promise in the leukemias, but further experience and testing of other compounds seems necessary before attempting to assay the value of nitrogen mustard therapy for the leukemias.

Mycosis fungoides. Only 3 patients with mycosis fungoides have been treated. In one patient with bulky generalized skin tumors the response was rapid and there resulted about a 75 per cent regression of the tumors. Relapse however was equally prompt, and a second course, which was almost followed by death of the patient with severe leukopenia, thrombocytopenia and purpura, was likewise followed by a partial regression, but again the relapse was rapid and the disease progressed steadily in a patient growing gradually weaker, and continuing to have anemia, leukopenia and a low platelet count so that neither further nitrogen mustard therapy nor any adequate amount of x-ray therapy could be risked.

To sum up, then, the present status of nitrogen mustard therapy for lymphomas and leukemias, as judged by our own experience and

what has been learned from others, the following may be said:

1. The nitrogen mustard compounds *used so far* have not cured, nor have they shown evidence indicating a possibility that they can cure, any form of lymphoma or leukemia.
2. Methyl-*bis* (β -chloroethyl) amine hydrochloride and *tris* (β -chloroethyl) amine hydrochloride, the two compounds almost exclusively tried up to now, may have marked palliative effects, particularly in Hodgkin's disease, in which especially the detoxifying effects on patients with generalizing disease may be gratifying and more easily accomplished than by x-ray therapy.
3. Remissions, when produced, are disappointingly short, as a rule. Some longer remissions have been produced in some cases by more aggressive dosage, that entailed hematological hazards that were unpleasant and sometimes dangerous.
4. For best effects on early strictly localized lymphomas, on lymphomas beginning to spread but still relatively regionally localized, and on bulky lymphomatous or leukemic masses, in general, local x-ray therapy is superior.
5. There is no basis for general competition between x-ray therapy and nitrogen mustard therapy. The availability of nitrogen mustards affords an additional means of therapy, useful for selected cases or stages of the disease, especially Hodgkin's disease.
6. To this summary should be added:
 - a) Early results of one and possibly two of the newer nitrogen mustard compounds indicate the possibility of better palliation of leukemia than with the methyl-*bis* or *tris* compounds.
 - b) The results already seen with these agents that were prepared primarily for chemical warfare rather than therapeutic purposes, and the fact that "literally hundreds of congeners remain to be synthesized and evaluated"⁶ offers distinctly the hope that, as has been true of chemotherapy for infections, other compounds far more effective therapeutically may be found.

It was of interest to observe recently in an advanced case of Hodgkin's disease treated by HN₂ an almost complete remission of quadriplegia, a result such as theretofore had been witnessed only following intensive local x-ray therapy to the spinal cord.

Stilbamidine (di-amidine-stilbene di-isethionate) and Pentamidine for Multiple Myeloma: Snapper,^{10, 11, 12} in recent communications has

reported the relief of pain in most cases of multiple myeloma by 15 or more intravenous or intramuscular injections of 150 mgm. of stilbamidine or 20 to 30 intramuscular injections of 100 mgm. of pentamidine, provided the patients were kept on a diet low in animal protein.

He found changes in the nucleoprotein of the cytoplasm of the myeloma cells in cases treated with stilbamidine, interpreted as precipitates of ribose nucleic acid, concludes that the metabolism of the myeloma cells is disturbed by stilbamidine, and infers that the abolition of pain is brought about by an arrest of proliferation of the myeloma cells in bone. In some instances partial recalcification and healing of bone lesions was observed.

In four of twenty patients treated with stilbamidine a late sign of intoxication was a dissociated anesthesia in the trigeminal area, beginning two and one-half to five months following the treatment.

Snapper advises great caution in use of the drug in patients with renal failure. He states that the treatment merely checks the disease, but does not cure it.

Urethane for Leukemia: Haddow and his group¹³ in testing the effect of carbamates, particularly urethane, on malignant neoplasms, noted that after protracted administration a leukopenia occurred. This observation suggested trial of this chemical in cases of leukemia.

They published a rather optimistic report of reduction in white cell counts, in size of enlarged spleens and relief of symptoms, and indicated greater effect on the less mature cells.

This report led to trials of urethane in this country. In general the effects have been rather unpredictable. In dosage of about 1 gm. three times a day in adults only moderate toxicity results (nausea, vomiting, and some drowsiness); but a good effect on the leukemia is found in only about one-third of the cases, and usually only after administration of the drug has been continued steadily for a month.

Radiation Therapy: In recent years radiation therapy of lymphomas and leukemias has been accomplished either by external irradiation with x-rays, by means of various techniques, or internal irradiation by means of radioactive isotopes.

The radioactive isotopes that have been used, in the lymphoma-leukemia field are chiefly radiosodium, radiophosphorus and radio-manganese. Of these, radiophosphorus has had the widest use, one of the reasons being that it has a sufficiently long half-life to permit its

shipment considerable distances without undue loss of radioactivity by decay, and another reason being that it is somewhat selectively picked up by the more rapidly growing cells of a leukemic or lymphomatous process. Radiosodium has such a short half-life that its use is confined to clinics near the source of supply. Since sodium is so uniformly distributed throughout the body fluids there is no selective pick up of radiosodium, and its effect, considering also its short half-life of about 15 hours, is more like that of a whole body spray of x-rays. Such a type of treatment may of course be useful in leukemia, and the lack of prolonged radioactivity effects may be at times advantageous.

Just as in chemotherapy of lymphomas and leukemias, barely a beginning has been made, so with the radioactive isotopes. When we consider that there are many whose biological properties and therapeutic possibilities remain to be explored, it seems quite possible that the next several years may witness the discovery of much more effective means of treatment with radioactive isotopes. Robley D. Evans' article¹⁴ in the book "Medical Physics" published 3 years ago listed about 400 radioactive isotopes that had been made by the cyclotron, and in "Science" in June, 1946¹⁵ there was published a list of about 100 isotopes, products of the uranium pile.

Radiophosphorus, or P³², formerly made in the cyclotron by the bombardment of phosphorus with deuterons (heavy hydrogen nuclei) is now available from Oak Ridge, and probably eventually will be made available from other uranium piles. P³² is so named to indicate that the atom of phosphorus, instead of having a mass of 31 has acquired a mass of 32 by the addition of one neutron to its nucleus, although the nucleus still has the same number (15) of protons or positive charges, and the same number of electrons are still revolving about the nucleus. Hence chemically P³² is identical with ordinary phosphorus, P³¹, and cells will accept P³² in their metabolic turn-over of phosphorus as readily as P³¹.

There are four reasons why radiophosphorus would seem theoretically to offer an approach to an ideal method of treatment of leukemia or lymphoma by irradiation.

1) Selective pick-up of phosphorus by the more rapidly growing cells of leukemia or lymphoma, so that each such cell becomes a source of radiation.

2) Total body distribution of this selective internal irradiation.

3) The half-life of 2 weeks, resulting in the irradiation of succeeding generations of cells over a reasonable period, but not entailing permanent storage of significant amounts of radioactive material as would be the case with a salt of radium, which has a half-life of 1,600 years.

4) The only type of radiation emitted by radiophosphorus is beta radiation having an average energy of 0.6 million electron volts and a maximum energy of 1.8 million electron volts. These beta particles penetrate tissue to an average of only 2 or 3 millimeters and to a maximum of about 7 millimeters.

Unfortunately, while this combination of features suggested the possibility of great efficacy in the treatment of lymphomas and leukemias, and some of the early results in the treatment of leukemia by P^{32} supported such a hope, it soon became evident that P^{32} was not producing cures of leukemia, that it was only moderately helpful in some cases of lymphosarcoma, and that it was not effective in most cases of Hodgkin's disease. Further clinical trials indicated that the shortcoming of P^{32} was simply that it was not sufficiently selective for the types of cells which one wished to affect and that in treating the tumor cells one was unavoidably also affecting normal marrow cells. Persistence in repetition of doses of P^{32} could lead to severe marrow depletion, while still the malignant process remained viable. One may reason that even if one assumed that P^{32} were selectively picked up only by leukemic cells and by no others whatsoever, the very fact that beta rays penetrate up to 6 or 7 millimeters into surrounding cells is sufficient reason to expect that depletion of the marrow would become, as it has been shown to be, the limiting factor in the treatment of leukemia by P^{32} .

Then, when we consider how much intensive local x-ray therapy may be required to cause regression in many cases of lymphosarcoma and Hodgkin's disease, it is easy to see why it is impossible safely to load up the patient's entire body with enough P^{32} to administer an effective therapeutic dose to the enlarged nodes, spleen, and other foci of lymphomatous disease. Much less feasible is it to attempt treatment of such processes as metastatic breast cancer, or osteogenic sarcoma by means of P^{32} . Yet inquiries still come in every week concerning the suitability of such cases as a localized myxosarcoma, or a metastatic melanoma for treatment by radiophosphorus!

Occasionally some very radiosensitive cellular neoplasm such as

metastatic teratoma of the testis has been found to respond temporarily with a good regression following the administration of P³². In leukemia, the acute processes are in general as unsuitable for P³² as they would be for whole body roentgen irradiation. The white cell count in such cases may fall rapidly, or local leukemic deposits may regress, but just as with treatment by roentgen rays, the course of the disease as a whole is not favorably affected and may very easily be aggravated.

In June 1945, Shields Warren¹⁶ reported his results in the treatment of 81 cases of leukemia during a period of over 4 years. He had selected cases chiefly of two unfavorable types; those which had become resistant to x-ray therapy after an initial favorable response, and those known to do badly with x-ray therapy, that is, acute leukemias of childhood, and a few moribund patients with chronic leukemia.

Of his sixty-six cases of leukemia, twenty-two had previously been treated, and these included seven cases of acute or subacute leukemia, and fifteen cases of chronic leukemia. In his previously untreated forty-four cases, there were 32 of acute, subacute or monocytic leukemia, and 12 cases of chronic leukemia.

Warren's best results were in the previously untreated chronic and subacute myeloid group, and, curiously, in the previously treated lymphatic group of all types.

An analysis of Warren's 1945 report should dispel any notion that good results were obtained in acute leukemia. From his tables it may be learned that of 9 cases of acute myeloid leukemia none were improved, of 12 cases of acute lymphogenous leukemia only 3 were helped, of 8 cases of unclassifiable acute leukemia none were considered improved, and of 4 cases of monocytic leukemia, none of which had previously been treated, only one was improved.

In February 1946, the Washington University group¹⁷ published an excellent detailed summary of the results of radiophosphorus treatment on a total of 155 cases including 30 cases of polycythemia vera, 94 cases of leukemia, six cases of Hodgkin's disease, nine cases of lymphosarcoma, two cases of mycosis fungoides, and eight cases of multiple myeloma. Thus, of their total of 155 cases, all but six were in the leukemia or lymphoma group, if one includes polycythemia in this group.

The St. Louis group's conclusions as to the value of P³² are in essential agreement with those of other writers. For polycythemia vera they

regard P³² as the best therapeutic agent available. In chronic myelogenous leukemia they reported that P³² produced at least as complete clinical and hematological remissions as x-ray treatment, and a suggestion of about an equal prolongation of life (about 6 months), with the advantage of freedom from radiation sickness. In acute and subacute myelogenous leukemia they observed very little effect on the clinical course. Similarly most cases of acute lymphatic leukemia or leukosarcoma failed to respond favorably. For chronic lymphatic leukemia they regard P³² as probably as satisfactory as, but no better than, x-ray treatment. Monocytic leukemia failed to respond to P³². Hodgkin's disease, lymphosarcoma, mycosis fungoides and multiple myeloma did not respond as well to P³² as to x-ray treatment.

At Memorial Hospital we recognized early in our work with P³² that it alone would not satisfactorily control most of the cases of leukemia, and that it was best regarded as not in competition with x-ray therapy, but as a complementary agent. Therefore, almost from the beginning of our work¹⁸ in 1940, most of the cases received x-ray treatment when it seemed indicated, and P³² when there seemed some good reason for its use. We have treated very few cases of Hodgkin's disease with P³² because early reports indicated a general agreement on the comparative lack of good results in that disease, and because experience with the amount of x-ray treatment necessary for effective control of Hodgkin's disease indicated the unreasonableness of trying to control it by P³². In a few cases of plasma cell myeloma P³² has failed in our hands to have any worthwhile result. In the treatment of lymphosarcoma for the past several years only an occasional case of an unusually radiosensitive type such as some of the follicular lymphosarcomas, is selected for a course of P³² as part of the treatment program.

The following tables, compiled by Dr. George H. Parks and Dr. Loton Rasmussen from our records, summarize the comparison of results with P³² and with x-rays in a series of cases of leukemia and lymphosarcoma in which both agents were used at different times.

In the treatment of a relatively small number of cases of polycythemia vera our own experience has been mostly with patients living at some distance, so that the hematological effects have not been followed as closely as was desirable. It has seemed that symptomatic improvement was greater than the hematological improvement, and whether results are better in this group than those obtained previously by spray therapy

CHRONIC LEUKEMIA

	<i>Myelogenous</i>	<i>Lymphatic</i>	<i>Total</i>
Cases Studied	27	27	54
P ²² and α -rays equally effective in producing remissions	15	9	24
P ²² more effective than α -rays in producing remissions	1	1	2
P ²² less effective than α -rays in producing remissions	5	2	7
P ²² used entirely or almost entirely in producing remissions	4	2	6
P ²² and α -rays both ineffective	0	2	2
P ²² produced remissions but too little used for comparison with α -rays	2	11	13
P ²² more useful because α -rays too toxic to be tolerated	1	0	1
P ²² less effective than α -rays in treating local manifestations	2	9	11

ACUTE AND SUBACUTE LEUKEMIAS

Total cases studied	31
Cases without remission	25
Cases with remission	6
Remission associated with P ²² therapy	2
Remission associated with α -ray therapy	2
Remission associated with acute infection and sulfonamide therapy	1
Remission spontaneous	1

LYMPHOSARCOMA

Total cases studied	19
P ²² and α -rays equally effective	2
P ²² more effective than α -rays	2
P ²² less effective than α -rays	10
P ²² used entirely or almost entirely in producing remissions	2
P ²² and α -rays both ineffective in producing remissions	3
P ²² more useful because α -rays too toxic to be tolerated	0
P ²² less effective than α -rays in treating local manifestations	11

or x-ray treatment of the long bones seems at present doubtful.

Recently attention was called to a belief apparently held by some physicians that treatment by means of radiophosphorus of a patient with polycythemia is likely to induce leukemia. It is fairly common for polycythemia to eventuate in myeloid leukemia or to present a leukemoid picture. In the Mayo Clinic series of 163 cases reported by Tinney, Hall, and Giffin,¹⁹ of 36 patients in whom the disease was of 5 or more years duration, death had occurred in 6 from leukemia or leukemoid reaction. I know of no evidence that has been produced to show that radiation causes or hastens conversion of polycythemia into leukemia, and it seems doubtful that this well-known mode of termination of polycythemia has any particular relation to irradiation. However, it would seem a project well worthy of careful statistical study, to compare cases treated only by phlebotomy, with those treated by phenylhydrazine, those treated by x-rays, by radiophosphorus, and by nitrogen mustards, since conceivably the repeated insults to the marrow by phenylhydrazine, x-rays, radiophosphorus, or nitrogen mustard might tend to evoke a leukemic response.

The following types of cases are the ones that seem most suitable for radiophosphorus therapy.

1. Polycythemia. Since there is a lag in the effect of P^{32} , a patient urgently in need of relief had best have phlebotomy at once.
2. Chronic myeloid leukemia with no marked enlargement of the spleen or liver. Bulky leukemic spleens or livers are probably best treated by local x-ray therapy and in general, the typical previously untreated case with a large spleen will obtain a better all around remission by means of x-ray therapy to the spleen.
3. Chronic lymphatic leukemia presenting rather minimal nodal, splenic and hepatic enlargement. Large nodes, spleens and livers will usually respond better to local x-ray therapy.
4. Cases requiring some maintenance therapy between courses of x-ray treatment may obtain some benefit from P^{32} .

5. Radiosensitive lymphosarcoma may perhaps be partially controlled as far as widespread minimal lesions are concerned, but local deposits of any considerable magnitude will be better controlled by local x-ray therapy.

Conventional Irradiation. Offhand one might think there is nothing to be said about recent advances with respect to conventional x-ray

therapy for leukemias and lymphomas. Certainly it is true that as far as the acute leukemias are concerned conventional irradiation has long been known to be ineffective and often dangerous. In the chronic leukemias, and in Hodgkin's disease and lymphosarcoma, however, considerably improved palliative results are now possible because of:

1. Increased knowledge of, search for, and detection and treatment of obscure lesions, formerly little known, but which are often of more importance to the morbidity of the patient than many of the more obvious lesions. Reference is made here to such lesions as those which may compress the spinal cord, to cortical bone lesions, to gastrointestinal lesions, and to pulmonary parenchymal deposits.
2. Greater precision in application of conventional irradiation to specific lesions with due attention to adequate inclusion of lesions in the beam of irradiation, adequate local dosage, and at the same time avoidance of unnecessary body dose, so as to spare the patient in so far as possible the deleterious effects on his marrow.
3. Recognition of the unicentric origin of many cases of Hodgkin's disease and of some cases of lymphosarcoma, so that early treatment of localized Hodgkin's disease or lymphosarcoma is carried out aggressively, giving the patient a chance, theoretically at least, for cure, certainly for longer palliation, than if just enough treatment is given to produce a regression.
4. Addition of a small dose, 75 to 125 r of total body irradiation in selected cases seems to have prolonged life and delayed relapse in some cases. The difficulty in this connection is in choosing the case in which benefit may be expected. Certainly we can look back and find cases so treated in which there seems to be no question but that they have had much longer remissions than were to be expected, had they received only local therapy.

A recent survey of the 5 year survival figures²⁰ for lymphomas and leukemias treated at Memorial Hospital from 1930 through 1940 shows in the main an improvement over previously reported results. Hodgkin's disease shows 20.5 per cent 5 year survivals of 283 patients, to be compared with 17.7 per cent of 265 patients treated from 1918 through 1935. Lymphosarcoma shows 26.3 per cent 5 year survivals of 308 patients, to be compared with 15.9 per cent of 132 patients treated from 1918 through 1933. Chronic lymphatic leukemia shows 15.7 per cent 5 year survivals of 125 patients, to be compared with a 5 year

survival of 9 per cent of a group of 77 patients with lymphatic leukemia treated from 1917 to July 1, 1929, from which group was excluded, however, only those cases lost to follow-up within 6 weeks. Chronic myelogenous leukemia shows the poorest survival rate—5.3 per cent 5 year survivals of 57 patients, to be compared with 5.9 per cent previously reported for 68 cases treated from 1917 to July 1, 1929. (Excluded from the latter group were those cases lost to follow-up within 6 weeks.)

These improved survival figures for all but myeloid leukemia reflect almost entirely the results of treatment by roentgen therapy and general supportive measures. They may serve in the future for comparison with results obtained by chemotherapy and isotope therapy.

Some mention should be made of the possibility of radical surgery for certain early and strictly localized cases of Hodgkin's disease and lymphosarcoma. Up to the present surgery in this field has been successful chiefly in certain gastrointestinal lesions, which perhaps have been somewhat atypical. Yet the evidence for unicentric origin of most cases of Hodgkin's disease and some cases of lymphosarcoma seems strong enough to suggest that the possibility of surgical removal should be kept in mind when an early localized lesion of a type that could be removed is found and no evidence of spread can be detected. Such cases are still so rare by the time a diagnosis is made that surgery will probably have to wait a good many years before it can come to play any large part in curative therapy.

To sum up the advance in the treatment of lymphomas and leukemias we may consider (1) what has been accomplished and (2) what seems to be promising.

What has been accomplished: (1) an improvement in palliative results measured both by relief of symptoms and by survival curves in Hodgkin's disease, lymphosarcoma and chronic lymphatic leukemia by roentgen irradiation as a result of greater precision in detection of lesions and in their treatment; (2) additional ways of palliation by means of nitrogen mustards for Hodgkin's disease, and some cases of lymphosarcoma and leukemia, by means of urethane for some cases of leukemia, and by means of stilbamidine for multiple myeloma.

What seems to be promising: (1) the possibility of cure of some cases of Hodgkin's disease and lymphosarcoma if diagnosis can be made early enough to permit obliterative roentgen therapy or perhaps even

radical surgery in cases amenable to such methods; (2) the possibility of development of more specific attack by means of suitable modification of radioactive isotope therapy; (3) the possibility of discovery of much more specifically acting chemotherapeutic agents.

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RELATION OF THE ADRENALS TO IMMUNITY*

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THE factors which contribute to immunity, both natural and acquired, have been recognized and partially evaluated as a result of experimental and clinical studies of the past sixty years. Among the more important of these factors are the following: 1) genetic, 2) cellular, 3) nutritional, 4) environmental, and 5) hormonal. The present discussion will be concerned chiefly with the relation of hormonal factors to immunity, with particular emphasis on the role of the adrenal cortex, although, as will be indicated, the level of functioning of the adrenal cortex is influenced markedly by at least two of the other factors, namely, nutrition and stimuli present in the environment. The term, immunity, will be used broadly with a connotation of increased resistance to both non-antigenic and antigenic substances, although a consideration of the relation of the adrenal cortex to immunity will be illustrated in part by antibody responses to specific antigens.

Evidence is available from both morphological and physiological studies that the adrenals play a significant role in the defensive mechanisms of the body, particularly against intoxications, infectious diseases and environmental stresses of the type of anoxia and abnormal temperatures. The active participation of the adrenal cortex in these circumstances has long been suspected by pathologists. Hyperemia, edema, hemorrhage, and focal necrosis occur in the adrenal glands in cases of burns of the skin, food or chemical poisoning, and acute infections. Conversely, adrenalectomized animals and patients with Addison's disease succumb readily to drugs, toxins, and stresses in amounts and degree generally innocuous to the normal individual.

Elucidation of the role of the *adrenal cortex* in immunity has been

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partially obscured by the numerous immunological studies with the hormone of the *adrenal medulla*, epinephrine, since it is now established clearly that epinephrine is a powerful augmentor of the rate of secretion of the hormones of the adrenal cortex.¹ The normal regulator of adrenal cortical secretion is the trophic hormone of the anterior pituitary gland, adrenotrophin. This pituitary hormone is secreted in greater than normal quantity following exposure of the organism to a wide variety of unrelated stimuli: inanition, alterations in environmental factors such as heat, cold and anoxia, trauma in the form of tissue injury, fractures and hemorrhage, injections of bacterial toxins, certain toxic chemicals (arsenic or benzene), anesthetics (nembutal), foreign proteins, and a variety of substances normally produced in the organism, e.g., histamine, insulin, epinephrine, thyroxine and estrogens.² The accelerated release of adrenal cortical hormones, as a result of any of these stimuli, does not occur in the absence of the pituitary, and each stress, therefore, has a common physiological influence, i.e., to increase the output of pituitary adrenotropic hormone. Thus, augmented secretion of epinephrine in the normal individual will elevate the rate of release of the pituitary adrenotropic hormone and result in an increased rate of secretion of the hormones of the adrenal cortex. There is, therefore, an intimate physiological relationship between the secretions of the two endocrine glands which constitute the adrenal, namely, the adrenal medulla and the adrenal cortex. As will be indicated, the available evidence suggests strongly that data establishing an increased immunity following epinephrine injection were probably a manifestation of the increased concentration of circulating adrenal cortical steroid hormones resulting from the ability of epinephrine to augment pituitary adrenotrophin secretion.

From the foregoing, it would appear that those physiological processes contributing to immunity and influenced or regulated specifically by adrenal cortical secretion will also be affected by any one of the variety of stimuli which augment pituitary-adrenal cortical secretion. This concept will aid in explaining the similarity of certain phenomena of immunity under widely diverse circumstances.

What do pituitary-adrenal cortical stimulation and the resulting increase in concentration of circulating adrenal cortical steroid hormones, contribute to immunity? This question can be answered in part in terms of the established physiological functions of these steroid hor-

mones, which affect several large categories of metabolic phenomena: 1) water and salt metabolism; 2) protein metabolism; and 3) carbohydrate metabolism. In addition, it has been demonstrated recently that adrenal cortical steroids contribute to certain aspects of immune cellular responses, namely, development of phagocytic cells and production of immune globulin. Whether these known physiological effects of pituitary-adrenal cortical secretion can explain completely the role of this endocrine mechanism in immunity is a problem under investigation in many laboratories.

Data obtained in collaboration with Dr. T. F. Dougherty³ show that the adrenal cortical steroids have a marked effect on cells long known to be concerned with certain processes of immunity, namely, reticuloendothelial cells. Increased numbers of phagocytic cells develop in lymphoid structures as a result of increased adrenal cortical steroid secretion or injection. The histological picture seen in these circumstances is similar in many respects to that observed following a single injection of a bacterial antigen.⁴

Another reticuloendothelial cell whose morphology and function are affected by adrenal cortical steroids is the lymphocyte. Lymphocyte dissolution and degeneration, with a resultant decrease or involution of lymphoid tissue, is known to occur following a wide variety of stresses. In many instances, this decrease in lymphoid tissue mass has been demonstrated to be based on the augmented rate of pituitary-adrenal cortical secretion caused by the stress. This is illustrated strikingly, for example, by the involution of lymphoid tissue which occurs in fasted animals but not in fasted animals which have been previously adrenalectomized.^{5,6}

In the normal animal, shedding of lymphocyte cytoplasm and lymphocyte dissolution may be accelerated as a consequence of increased pituitary-adrenal cortical secretion,³ and the constituents of this cell thus released to the lymph and eventually participate in metabolic transformations.^{7,8} One of the constituents of lymphocytes has been demonstrated to be identical with the normal serum gamma globulin.^{7,8,9} In the immunized animal, this fraction of the serum proteins frequently contains antibody, and it has now been demonstrated that the lymphocytes of the immunized animal contain antibody.^{10,11} The release of protein from lymphocytes, and perhaps other cells, as a result of an increased concentration of circulating adrenal cortical steroids

may be an important aspect of the contribution which these hormones make to carbohydrate formation from protein.

It should be emphasized that hormones affect the rates of physiological reactions which may continue, albeit at a slower than normal rate, in the absence of the endocrine secretions. Removal of the thyroid gland does not result in a complete cessation of metabolism, but reduces it to a much lower rate or level. Also, experimental removal of the pituitary gland, which exerts a profound control over certain other endocrine organs, does not prevent life from continuing for almost normal periods of time, although again at a greatly reduced operating level. Conversely, the release in the organism of excessive amounts of certain endocrine products, or increasing their concentration by administration from without, results in acceleration of reactions normally influenced by those hormones. This is seen, for example, in data demonstrating that injection of adrenal cortical steroids, or increased secretion of these hormones as a result of pituitary adrenotrophin injection, produces an elevation of antibody titer either in a hyperimmunized animal or in a previously immunized animal with no circulating antibody.^{8,12,13} These experiments suggest that the physiological basis of the anamnestic response is the pituitary-adrenal cortical control of lymphocyte structure and function. This would explain why various unrelated stimuli produce an anamnestic response. The maximum increase in antibody titer in the blood occurs at a time after hormone injection when the degree of lymphocyte dissolution is maximal. On the other hand, it has been observed recently that antibody production does not cease in the adrenalectomized animal.^{14,15}

The results which have been obtained establish a partial basis for the role of the adrenal cortex in immunity, with particular reference to antibody formation. It may be pointed out that antibody production may be of two types: 1) that resulting from the reaction of the antigen with cells of the reticuloendothelial system, and 2) that arising as a result of the proliferation of antibody-containing cells, i.e., lymphocytes.¹⁶ It is not unlikely that the equilibrium which obtains between these two types of antibody production in the normal organism may be altered in both the hormone treated and the adrenalectomized animal. Moreover, the data which have indicated a role for the adrenal cortex in antibody production have considered only one aspect of the problem, namely, antibody release from lymphocytes. It should be emphasized

that the concentration of antibody in the circulation at a particular time is probably a reflection of a state of dynamic balance among at least three metabolic processes involving antibodies: 1) synthesis, 2) release from antibody-containing cells, and 3) peripheral removal or utilization. It remains for future investigations to evaluate fully the contribution which each of these reactions makes to determining the level of circulating antibody under a variety of circumstances. Hormonal secretions could influence the rates of all of these processes, and removal of an endocrine gland may result in antibody production rates which are not necessarily the antithesis of those seen following injection of the hormone produced by that gland.

The demonstration that the lymphocyte is one of the end cells of adrenal cortical steroid action serves to integrate the role of the lymphocyte and the adrenal cortex in resistance. The control exerted by pituitary-adrenal cortical secretion over the contribution of the lymphocyte to immune globulin production is related to a specific type of resistance, immunity based on antibody formation. Whether this endocrine-lymphocyte relationship contributes to other types of resistance or immunity remains to be investigated. It is possible that the spontaneous involution of the adrenal cortex in man which begins during the second week of extra-uterine life may be the causative factor of the lowered immunity in infants during this age period. The value of adrenotrophin or adrenal cortical steroids, or of a physiological non-specific stimulus of the type of very small doses of epinephrine, as a method of increasing immunity in the human, is worthy of study and remains to be evaluated clinically.

In conclusion, a few comments may be made regarding the role of certain other endocrine glands in immunity. Clinical and experimental evidence has suggested that thyroid secretion is concerned with lymphoid tissue growth, and since this tissue is apparently an important site of antibody formation, the thyroid gland may contribute to at least a specific type of immunity. Evidence is now available that lymphoid tissue growth, after involution of these structures, is retarded in the absence of the thyroid.^{6,15} Finally, the role of the sex hormones in immunity may now be interpreted, in part, in terms of the effects of these hormones on pituitary-adrenal cortical activity. Physiological doses of estrogens will generally augment, while larger amounts of estrogens produce inhibition, of pituitary adrenotrophin secretion. Androgen ad-

ministration will also generally diminish pituitary-adrenal cortical activity. It is not unlikely that sex differences in immunity, both natural and experimentally produced, may be related in part to the diverse actions of estrogens and androgens in influencing the level of pituitary-adrenal cortical secretion. The endocrine glands and their hormonal actions exhibit a high degree of integration and correlation in metabolism. As a consequence, the endocrine response to a particular stress may affect many diverse physiological processes which contribute to the immunity of the organism. Investigations of these processes in relation to endocrine secretions will make possible a more complete evaluation and understanding of the phenomena of natural resistance, of which immunity is one important aspect.

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CLINICAL AND EXPERIMENTAL STUDIES ON ADRENAL CORTICAL HYPERFUNCTION*

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THE adrenals in mammals and man consist of two glands united together. The two component parts, the medulla and the cortex, are developmentally and histologically entirely unrelated and are derived from two distinct and different parent tissues which unite only secondarily. The cortex is derived from the mesoderm and is closely associated with the urogenital mass, while the medullary tissue is derived from the ectoderm and has a common origin with the cells constituting the sympathetic nervous system. Although the cortex and medulla exercise entirely different functions, the recent studies of Long and his group indicate that the activity of the cortex is at least to some extent influenced by the functional integrity of the medulla. This relationship is evidenced by the fact that the medullary secretion, epinephrine, causes a release of adrenocorticotropic factor from the anterior lobe of the pituitary gland, which in turn stimulates the adrenal cortex.

The adrenal cortex is an organ of many functions. It plays a very vital role in salt and water and carbohydrate metabolism. It is intimately concerned with growth and muscular response. Evidence has been accumulating to indicate that it is important in the maintenance of normal blood pressure, and that it is probably very significant in the pathogenesis of certain types of hypertension. It has long been established that this organ is essential in resistance to stress and more recently that it is of prime importance in immunological responses. In addition it exercises a profound effect on the functions of other endocrine glands, notably the thyroid, gonads, and anterior lobe of the hypophysis. In short, the adrenal cortex plays a most active and important part in many vital bodily functions. Indeed, it is essential to life and its complete ablation, either experimentally or clinically, results

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in death unless substitutive therapy is administered.

The experimental removal of the adrenal glands in animals, or their total destruction through disease in man, results in a fairly well defined clinical picture which in effect represents the total disorganization of those functions which are normally dependent on the integrity of the cortex. Thus there occurs the usual loss in sodium with its attendant fluid loss, the characteristic disturbance in carbohydrate metabolism with either overt or subclinical hypoglycemia, the hypotension and asthenia, the increased susceptibility to infection, and the marked intolerance to stress. But in approaching the problem of adrenal cortical hyperfunction the situation is quite different and infinitely more complicated. This difference is in part due to the fact that there is no one hormone or mixture of hormones which actually represents complete replacement therapy. This lack renders it impossible at present to induce experimentally a state of adrenal cortical hyperactivity in its entirety. The most that one can accomplish with the hormones available is to note their individual effects when injected into normal or adrenalectomized animals. Although the information thus gained is important, it is by no means adequate since many of the signs and symptoms observed in patients with adrenal cortical hyperfunction cannot be experimentally duplicated. It is reasonable to expect, however, that with the further isolation of adrenal cortical fractions this problem will become progressively more clarified. Until such time we must utilize, in addition, the information obtained by the investigation of clinical material.

Here, too, however, the problem is complicated by the diversity of manifestations presented by patients with adrenal cortical hyperfunction. This lack of a consistently uniform clinical picture is probably due to the fact that the adrenal cortex consists of several different types of cells with varying functions. Thus, the studies of Greep and Deane and their co-workers strongly suggest that the zona glomerulosa is concerned with the elaboration of the salt and water hormone, while the work of Blackman, although much less conclusive but also provocative, points to the reticular zone as the origin of the sex hormones. It would appear, therefore, that the signs and symptoms presented by the patient are dependent on which cells are involved and stimulated by the hyperplastic or neoplastic process and which are destroyed by the same process with a consequent loss of their secretions.

The best clinical example of adrenal cortical hyperfunction is provided by the patient with an adrenal cortical tumor. This disease may then be used as a starting point from which to study the disturbance in physiology resulting from adrenal cortical overactivity. With this as a point of departure it promptly became apparent that a variety of pathological processes located in the adrenal or elsewhere were capable of producing a picture indistinguishable from that observed in patients with adrenal tumors. The point to be emphasized is that whether the basic disease process is an adrenal cortical tumor or hyperplasia, or a pituitary or thymic tumor, or hypothalamic disease, their respective clinical effects are mediated essentially through the adrenal cortex.

In a broad sense, the manifestations of cortical hyperfunction fall into two large categories consisting of 1) sexual, and 2) metabolic abnormalities. The sexual disturbances are characterized by pseudohermaphroditism, precocious sexual development, the development of hirsutism, changes in the voice, enlargement of the clitoris, decrease in the size of the breasts and amenorrhea in the females, while feminization and loss of libido are observed in adult males. The metabolic aberrations consist of the appearance of marked obesity which is generally curiously distributed, hypertension, plethora, disturbances in carbohydrate metabolism, osteoporosis; the appearance of purplish striae on the abdomen, flanks, breasts, arms or thighs, polycythemia, acne, and the development of a characteristic moon-like facies. The symptoms of the first group are generally referred to as the adrenogenital syndrome, while those of the second group are known as the Cushing syndrome. Patients with adrenal cortical disease may manifest predominantly the adrenogenital syndrome, the Cushing syndrome, or a combination of both. The sharp emphasis on the distinction between the two groups of symptoms is by no means entirely of academic interest. The distinction is of considerable practical significance, since the ultimate prognosis is considerably affected by these considerations. The life span of the patient who shows virilism alone is considerably longer and the outlook very much better than is the case with the patient who shows evidence of Cushing syndrome. In the latter group the contralateral adrenal is always atrophic either grossly or functionally, and the operative risk associated with the removal of the tumor is prohibitively high. On the other hand, in those patients with an adrenal cortical tumor whose major manifestation is virilism, the con-

contralateral adrenal is perfectly normal, and the removal of the tumor can be effected without any grave operative hazards. The operative mortality following the removal of the tumor in patients with Cushing syndrome is also influenced by the character of the tumor. The removal of a malignant tumor is much less hazardous than that of a benign one. The probable reason for this is that in the former group metastases occur early and by the time surgical removal is attempted viable metastases are already present.

The clinical picture which develops with adrenal cortical hyperfunction is in part dependent on the age and sex of the patient. When adrenal cortical hyperplasia or tumor occurs in utero in females, pseudohermaphroditism usually results. Pseudohermaphroditism is characterized by the presence of the gonads of only one sex, but associated with this are such abnormalities of the external genitalia as to render the identification of the sex through external examination doubtful. Frequently, pelvic inspection of the gonads has to be resorted to in order to establish the sex of the patient. Pseudohermaphroditism should not be confused with true hermaphroditism, since the latter is an embryological defect unrelated to any abnormalities of the adrenal cortex and characterized by the presence of the gonads of both sexes in the same person.

When the disease develops in children up to the age of puberty, the resulting clinical picture is quite different. Female children thus afflicted may manifest sexual precocity, the development of hirsutism of the face and limbs, enlargement of the external genitalia and breasts and deepening of the voice. Occasionally the only or major manifestation may be unusual obesity. In most instances there is a temporary period of rapid growth. This is, however, followed by an early closure of the epiphyses, and the patient generally remains short in stature. Menstruation as a rule does not occur even in older children who may have attained puberty, although several notable exceptions have been reported.

Male children with this illness generally show marked muscular and sexual development. They grow rapidly, develop signs of virilism with excessive hirsutism of the face, arms, and pubis. The size of the genitals may assume adult proportions. Genital maturation as a rule does not occur, although spermatogenesis has been observed. Occasionally, as with girls, obesity has been the outstanding manifestation of

the disease. The metabolic disturbances characteristic of Cushing syndrome are not infrequently observed in children along with the sexual abnormalities.

The clinical picture in women is usually characteristic and readily identified. They develop obesity which is generally limited to the face, upper part of the back, and the abdomen. The upper and lower extremities remain thin. The face assumes a rounded puffy plethoric appearance, described as "moon-like." There is an excessive growth of hair on the face, extremities, and abdomen. The breasts shrink in size, the clitoris may enlarge, amenorrhea develops, and the general muscular and skeletal configuration may approximate that of the male. The voice becomes deep, due to the elongation and thickening of the vocal cords. There is generally a loss of libido, but not infrequently their sexual interests are diverted to other females. In addition they may manifest hypertension, generalized osteoporosis, striae, polycythemia, and acne. The disturbance in carbohydrate metabolism is characterized by the presence of hyperglycemia, glycosuria, and a diabetic glucose tolerance curve. In short, these patients generally present a fully developed picture of both the adrenogenital and Cushing syndrome. Occasionally the predominant picture is that of virilism with little or none of the Cushing counterpart.

Adrenal cortical hyperfunction in adult males usually results in the production of Cushing's syndrome with some feminization, or they present signs of marked feminization with comparatively few manifestations of the metabolic abnormalities. Thus, they may show a thinning of the hair, the skin becomes delicate and soft, the genitals decrease in size, and there is a loss of libido. In many instances the breasts become quite large, and rarely a milky colostrum-like fluid is secreted. It is of interest, that while prepuberal boys, girls, and women all show signs of marked virilization, in adult males some degree of feminization is the rule.

These, then, in brief are the clinical syndromes produced by adrenal cortical hyperfunction. The fact that disease of the adrenals is capable of inducing such marked and unusual physical changes dealing with very fundamental processes attests to the primary role that they play in the body economy. With the biochemical techniques available to-day these syndromes present a unique opportunity to unravel the physiological role of these organs.

The adrenal cortex is the site of manufacture of three large groups of hormones: 1) Those dealing with electrolyte and water metabolism; 2) Those dealing with carbohydrate and protein metabolism; and 3) The sex hormones. There are many factors which influence the secretory activities of the adrenal cortex, but all of these factors operate through mediation of the anterior lobe of the hypophysis. In addition, the adrenal cortex is capable of autonomous function. It is true that following the experimental removal of the anterior hypophysis adrenal cortical activity is seriously impaired, but it is not entirely lost. This point is important if we are to explain the clinical picture resulting from an adrenal cortical tumor. The actual increase in size of the adrenal mass results in an increase in formation of the various cortical fractions, and hence the production of the characteristic syndrome. It is in effect immaterial as to whether the total increase in hormone is due to an actively secretory local tumor or due to increased secretory activity resulting from stimulation by the adrenocorticotropic factor of the anterior pituitary. The point which is important is that the clinical picture is determined by the amount of adrenal cortical hormone or hormones formed. It is on this basis that we can understand why the adrenogenital-Cushing syndrome may be produced by such superficially widely differing pathological processes as basophil tumors of the pituitary, malignant thymomas, tumors of the adrenals, and perhaps disease of the hypothalamus.

The sex hormones which have actually been isolated from the adrenal cortex of experimental animals are adrenosterone, 11-hydroxyisoandrosterone, 17-hydroxyprogesterone, and theelin. These compounds, with the exception of theelin, have androgenic activity, while the latter has a pronounced estrogenic effect. It does not necessarily follow, of course, that these hormones are identical with those elaborated by the human adrenal. This is a point difficult to prove, since it hardly lends itself readily to experimental study. The occasional attempt to isolate active sexual fractions from hyperplastic and tumorous adrenals has resulted in extremely meager yields. This may be due either to the fact that the present techniques are not adequate for the limited material available, or that only minute amounts of these substances are stored in the gland where they are manufactured. However, that the adrenals do manufacture such hormones is suggested by the marked decrease in the urinary excretion of various androgenic and estrogenic com-

pounds which follows the successful removal of an adrenal cortical tumor, or which occurs when the adrenals are destroyed by some pathological process, as in Addison's disease.

Under normal circumstances androsterone, dehydroisoandrosterone 3α -hydroxyetiocholanone-17, pregnadiol, and estrogens are excreted in the urine. Of these, the first two have definite androgenic activity while the 3α -hydroxyetiocholanone-17 is inert. These compounds have their origin in both the adrenal cortex and the male gonads. It has not been established that these are actually the compounds elaborated by the adrenal cortex. It is more likely that they represent degradation products of parent substances elaborated by the glands. In the presence of adrenal cortical hyperfunction not only is there usually an increase in the urinary excretion of these compounds but several additional ones have been isolated, including isoandrosterone, $\Delta_{3,5}$ androstadiene-17-one, 3α -hydroxyandrosterone-17, and pregnane- $3,17,20$ -triol. Of these compounds only the pregnane triols are probably inert.

The increase in the urinary excretion of both androgenic and estrogenic fractions which occurs in adrenal cortical hyperfunction is due to the excessive formation of these or parent substances. In the light of these observations one might expect that the degree of virilism or feminization displayed by the patient could be correlated with the urinary excretion of androgens and estrogens. But, surprisingly enough, such correlation does not always occur. Patients with virilism may excrete normal amounts of androgen, or even excessive quantities of estrogen. In some instances of adrenal cortical carcinoma with virilism, excessive quantities of androgen are excreted in the urine, and in at least one instance of marked feminization in a male due to a malignant adrenal tumor large amounts of estrogenic hormone were noted in the urine. However, even larger quantities of urinary estrogens have been observed in masculinized women. These observations are disconcerting, but it should be remembered that what we measure in the urine probably represents an overflow and is not necessarily an index of the amount of hormone actually utilized by the body. The thesis that virilism or feminization is due to excessive formation of the corresponding sex hormones is a reasonable one. The evidence, although admittedly confused and frequently contradictory, is at least suggestive.

The early observations dealing with adrenal cortical physiology demonstrated the significance of this organ in relation to electrolyte

metabolism, particularly the metabolism of sodium and water. With the experimental or clinical destruction of the adrenal cortex there occurred a loss of sodium from the intercellular tissue spaces, with a proportionate loss of fluid. There followed a loss in chlorides, an increase in serum potassium, and a reduction in CO_2 content. These electrolyte and fluid abnormalities were promptly corrected by the use of whole adrenal cortical extract and even more specifically so by the crystalline fraction—desoxycorticosterone. Further fractionation studies of adrenal cortical extract revealed that not all of the fractions isolated exercised a salt-retaining effect. Indeed, some compounds like 17-hydroxy-11-dehydrocorticosterone and 17-hydroxycorticosterone exercised a salt diuretic effect, while others, like corticosterone and dehydrocorticosterone, have only a minimal salt retaining effect. Desoxycorticosterone has no effect on carbohydrate metabolism, while those compounds like corticosterone, dehydrocorticosterone, and 17-hydroxycorticosterone which have either no effect on electrolyte metabolism or actually cause a salt diuresis, exert a marked effect on carbohydrate metabolism. The essential structural difference between compounds causing salt retention and those influencing carbohydrate metabolism is the presence of an oxygen atom at C₁₁ in the latter instances. The presence of this oxygen, or hydroxyl group on C₁₁, while increasing the carbohydrate effect of the molecule, reduces its salt retaining effect. The salt diuretic fractions evidence a further structural difference in that they have an hydroxyl group on C₁₇.

In view of the fact that the adrenal cortex normally elaborates such hormones, one might expect evidence of increased secretion of these fractions in clinical instances of adrenal cortical hyperfunction. As a matter of fact Anderson and Haymaker have demonstrated that extracts of the blood and urine of such patients were capable of prolonging the lives of adrenalectomized rats beyond the survival period of untreated controls. The salt retaining effect of 1 cc. of blood was found to be equivalent to 4 to 6 grams of fresh adrenal tissue. It is, therefore, surprising that electrolyte abnormalities do not occur consistently. Actually, an increase in serum sodium occurs in approximately 15 to 20 per cent of the cases, while a reduction in serum potassium is demonstrable in 25 per cent. As to whether a disturbance in the electrolyte pattern occurs in clinical cortical hyperfunction is probably dependent on two factors: 1) Whether those adrenal cortical cells which are con-

cerned with the secretion of the electrolyte fractions are involved in the hyperfunctioning process, and 2) A compensatory mechanism is unquestionably set up, which in some way minimizes or inhibits the effect of these hormones when they are being secreted in excessive amounts. A clue as to the nature of this compensatory mechanism is provided by some experimental studies conducted in our laboratory. It was observed that in normal individuals and in patients with Addison's disease the intravenous injection of salt following the intramuscular injection of a single dose of desoxycorticosterone resulted in a retention of injected salt above that which occurs following the injection of salt alone. Similar experiments, repeated in patients with Cushing's syndrome on the other hand, resulted in a salt diuresis. Here, then, is the curious paradox of a hormone which under one set of circumstances causes a salt retention which is its expected and orthodox effect, while under other circumstances it produces a salt diuresis. It would seem then that in some instances of adrenal cortical hyperfunction the injected desoxycorticosterone either stimulates the secretion of a salt diuretic fraction or is itself converted into such a fraction. In view of the close chemical similarity between the salt retaining and the salt diuretic hormones, such a conversion appears quite feasible.

Clinically various electrolyte disturbances may be observed in hypercorticalism. There may occur an increase in blood sodium with or without an associated reduction in serum potassium and chlorides, or these latter changes may be present alone. A pathognomonic change, which is however only infrequently observed, consists of a reduction in serum chlorides and potassium, an increase in serum sodium with a marked alkalosis. The alkalosis, with the lowered chlorides and potassium may also occur with a normal serum sodium level. It is interesting to note that when a reduction in chlorides occurs this is always associated with a decrease in the blood potassium level. This is in contrast to the condition ordinarily observed in Addison's disease in which the chlorides vary with the sodium level and are entirely independent of fluctuations in the potassium values. In hypercorticalism the fluctuations of serum chlorides closely parallel those of the potassium. The administration of potassium either parenterally or orally will result not only in an increase in serum potassium but also that of chlorides, while the administration of chlorides will affect the serum levels of neither ion.

While serum electrolyte disturbances occur in somewhat less than

half the patients with adrenal cortical hyperfunction, alterations in carbohydrate metabolism occur more frequently, although by no means uniformly. The patients may develop frank hyperglycemia with glycosuria, or, much more commonly, the disturbance may be less overt and be manifested only by an abnormal glucose tolerance curve which assumes a diabetic pattern. The diabetes of adrenal cortical hyperfunction is difficult to control, since it is not as readily responsive to insulin and to the usual dietetic measures as in the case with true diabetes. On the other hand, severe diabetic ketosis has not been observed in this disease.

The disturbance in carbohydrate metabolism is probably dependent upon two factors. The first is the relation of the adrenal cortex to protein catabolism, and the second is the effect of the various adrenal cortical fractions on the peripheral oxidation and utilization of glucose. Since the adrenal cortex normally manufactures hormonal fractions which influence carbohydrate metabolism, it is a reasonable assumption that the disturbance in carbohydrate metabolism observed in hypercorticalism is due to excessive formation of these fractions. It is essentially immaterial whether the increased formation of these hormones is due to an increase in the number of the secretory cells such as occurs in adrenal tumors or whether it is due to increased secretory activity of the adrenal cortical cells secondary to the stimulating effect of adrenocorticotropic hormone of the adenohypophysis. The end result in both conditions is the same, in that larger amounts of cortical carbohydrate fractions are formed.

The adrenal cortex plays an important role in the breakdown of tissue protein and its conversion into glucose and glycogen. The brilliant work of Houssay and Biossoti, Long and his co-workers, Cori and Cori, Britton and Silvette, and Evans have clarified the nature of the mechanism involved. Fasting adrenalectomized rats excrete much less nitrogen than do normal rats under similar circumstances. The administration of cortical extract or its crystalline carbohydrate fractions results in not only an increase in liver glycogen and glucose but there is in addition a parallel and proportionate increase in urinary nitrogen. Since these changes occur under fasting conditions in both normal and adrenalectomized animals, it follows that both the increase in carbohydrate stores and the urinary nitrogen are due to the endogenous breakdown of protein. An even clearer demonstration of this phenomenon is provided by phlorhizin experiments. Phlorhizin lowers

the renal threshold for glucose so that sugar is excreted in the urine as long as there are available sources of sugar, be these sources endogenous or exogenous. Under normal circumstances glycosuria occurs even in the fasting animal. However, in the adrenalectomized phlorhizin treated animal glycosuria is markedly diminished. The administration of adrenal cortical extracts to such animals despite the continuation of the fast results in a marked increase in the glycosuria with a proportionate increase in urinary nitrogen.

The further effect of the adrenal cortex and its crystalline fractions on carbohydrate metabolism is provided by the studies on hypophysectomized and depancreatized dogs. The diabetes resulting from ablation of the pancreas is favorably modified either by the removal of the hypophysis or by bilateral adrenalectomy. The administration of anterior pituitary extract or adrenocorticotropic factor causes a reappearance of glycosuria and hyperglycemia provided the adrenals are intact. In the absence of the adrenals, no such effect is evident. However, the administration of adrenal cortical extract to the depancreatized animal will induce glycosuria and hyperglycemia both in the hypophysectomized and in the adrenalectomized state. The glycosuria, here too, is associated with a parallel increase in the urinary excretion of nitrogen. In the light of these studies the conclusion is inescapable that at least part of the effect of the adrenal cortex on carbohydrate metabolism is related to its ability to break down proteins and help in their conversion to glycogen and glucose. That this phenomenon occurs in an exaggerated fashion in patients with adrenal cortical hyperfunction is evidenced not only by the disturbance in carbohydrate metabolism but also by the fact that these patients are in negative nitrogen balance indicating excessive tissue destruction.

The second important factor in the disturbance in carbohydrate metabolism in Cushing's syndrome is related to the peripheral utilization of glucose. Certain adrenal cortical fractions, notably 17-hydroxy-11-dehydrocorticosterone, inhibit the utilization of sugar by the peripheral tissues. The administration of this compound to adrenalectomized-depancreatized dogs results in an increase in glycosuria not accompanied by a proportionate increase in urinary nitrogen, indicating that part of the glycosuria is due to the inability of the tissues to utilize glucose satisfactorily.

In the light of these observations, the refractoriness of the diabetes

in Cushing's syndrome becomes understandable. There is a constant available source of endogenous glucose which is not capable of being entirely oxidized by the tissues. Dietary restrictions would appear futile in view of the fact that endogenous glucose is being formed excessively, while the effect of insulin is minimized by the peripheral action of the cortical hormones.

Osteoporosis, so commonly seen in Cushing's syndrome, is probably a reflection of the disturbance in carbohydrate metabolism. It was originally assumed that the osteoporosis was due primarily to the effect of the pituitary on the parathyroid bodies. It was thought, therefore, that the presence of decalcification was evidence of the absence of an adrenal cortical tumor and favored the diagnosis of primary pituitary disease. With the accumulation of more clinical material it became evident that osteoporosis occurred with equal frequency in both primary and secondary adrenal cortical hyperfunction. Histological and biochemical studies have failed to reveal any evidence of true parathyroid abnormalities. In the early stages of the disease hypercalcinuria is occasionally observed, but in general the calcium balance studies are quite normal. This is equally true of the blood calcium and phosphorus levels. The histology of the bony changes observed in Cushing's syndrome is quite different from that of those seen in hyperparathyroidism in that the former never manifest the cystic changes and giant cell tumors so characteristic of the latter. In addition, there is no evidence of any reparative process in the bones in Cushing's syndrome, while some new bone formation does take place in the osteoporotic areas produced by parathyroid tumors.

There are probably two factors responsible for the osteoporosis in hyperadrenal corticalism. As was originally pointed out by Albright, the excessive protein breakdown and conversion into carbohydrates causes a depletion in the formation of bone matrix which is essentially a protein substance. This lack of bone matrix limits the amount of calcium which can be deposited for the formation of new bone. In addition, there is a failure to absorb sufficient calcium and phosphorus from the intestinal tract to permit retention of these ions. Because of this, some calcium and phosphorus are actually withdrawn from the bony skeleton to make up for this lack. Thus, there is not only impairment in the ability to absorb the necessary basic ions for the manufacture of bone, but there is an inability to deposit these substances for their proper utilization.

The large majority of patients with Cushing's syndrome have osteoporosis, although the degree of decalcification may vary considerably. The osteoporosis may involve the skull, ribs, spine, and, less frequently, the long bones. The decalcification in these structures may be mild and roentgenologically questionable, or it may be severe enough to produce spontaneous fractures of the ribs and compression fractures of the vertebrae. In general, the osteoporosis observed in Cushing's syndrome is not particularly characteristic and is indistinguishable from that produced by other causes. The only exception to this are the changes described by Sussman and Copelman occurring at the anterior ends of the lower ribs just lateral to the costochondral junction. The rib in this region is expanded to about twice its normal diameter and is homogenously increased in density. This increase in density is reminiscent of that observed in callus formation, and actually cannot be distinguished from the latter roentgenologically, although no fracture line is demonstrable. These changes in the ribs are observed very infrequently, but when present are very suggestive of Cushing's syndrome.

Hypertension occurs almost uniformly in patients with hyperadrenalcorticalism. The causal mechanism of the hypertension is obscure, but we may speculate profitably concerning the role of certain of the adrenal steroids in this respect. Desoxycorticosterone, one of the adrenal cortical fractions, is capable of producing hypertension when given in relatively large amounts over a prolonged period of time. This effect is observed in the normal and in the bilaterally adrenalectomized animal, as well as in normal individuals and in patients with Addison's disease. It is of interest, however, that this hypertensive effect is elicited much more readily in the absence of adequate adrenal function than in normal individuals or animals. The fact that elevations in blood pressure following the use of desoxycorticosterone, occur more readily in the presence of destroyed or ablated adrenals suggests that some compensatory mechanism is operative under normal circumstances which inhibits to some degree the hypertensive effect of this hormone. The nature of this substance is at present unknown. Whole adrenal cortical extract, which is a combination of various adrenal cortical fractions, is, however, incapable of inducing hypertension. This would suggest that the inhibitory factor is in all probability an hormonal product of normal adrenal cortical activity. It may be postulated that the hypertension in Cushing's syndrome is due either to the excessive manufacture of a

hypertensive fraction or the reduction in formation of the inhibitory or balancing hormone. It is possible that the hypertensive factor is a desoxycorticosterone-like compound, since this is the one adrenal cortical steroid, isolated to date, capable of producing abnormal elevations in blood pressure.

The hypertension in Cushing's syndrome may reach alarming levels. When it has persisted for a considerable time, secondary eye ground, renal, and cardiac changes take place. In that event the associated phenomena are no different from those observed in the usual severe hypertensive cardiovascular disease. Narrowing and nicking of the retinal vessels, exudates and hemorrhages are frequently observed in the fundi. Renal and cardiac failure, as well as cerebral accidents, may occur. Experimentally, with desoxycorticosterone, Selye and Hall have succeeded in producing renal changes in fowl and mammals similar to those seen in nephrosclerosis.

The diagnosis of adrenal cortical hyperfunction is based on the history, the physical appearance of the patient, and on certain laboratory procedures. It should be emphasized that not all patients who have hirsutism or who are obese have overt adrenal cortical disease. If these manifestations indicate some degree of adrenal cortical overactivity, they represent physiological variants. In patients in whom the history and physical examination suggest the possibility of this disease, the following laboratory determinations are available to aid in establishing the diagnosis: 1) Determination of blood electrolytes, particularly Na, Cl, K, and CO₂; 2) The salt tolerance test; 3) Colorimetric determination of the neutral urinary 17-ketosteroids and 11-oxyketosteroids; 4) The biologic assay of the urinary glucocorticoids; and 5) The demonstration of an adrenal mass by intravenous pyelography or by peri-renal insufflation.

Some abnormality in the blood electrolytes will occur in half the instances of adrenal cortical hyperfunction. The absence of such abnormalities does not mitigate against the diagnosis. A considerable increase in serum sodium or depression in serum potassium bespeaks adrenal cortical hyperfunction but does not help in localizing the pathology or in differentiating between tumor and hyperplasia. The salt tolerance test is significant only when positive—that is when the injection of desoxycorticosterone and salt under controlled conditions results in a sodium and chloride diuresis—and in that instance the result is

pathognomonic of adrenal cortical hyperfunction. As is the case with the blood electrolytes, the salt tolerance test is of no value in determining the nature or locus of the underlying pathology.

The term "17-ketosteroid" applies to those steroids with a ketone group on the 17th carbon atom. These neutral 17-ketosteroids form the urinary products of androgenic metabolism and arise from substances produced by the adrenal glands and the male gonads. They are further divided into alpha and beta fractions, which refer to the spatial position of the 3-hydroxyl group. The beta ketosteroids are readily precipitated by digitonin and are thus separated from the alpha members. The latter substances are elaborated by both the adrenal cortex and the male gonads, while the beta fractions are manufactured entirely by the adrenal cortex. In normal individuals only 10 to 15 per cent of the total urinary ketosteroids consists of the beta fraction. In normal urines the alpha ketosteroids include androsterone and 3- α -hydroxyacetocholanone-17, while the beta ketosteroids include dehydroisoandrosterone and isoandrosterone.

The daily urinary excretion of total neutral 17-ketosteroids varies with the age and sex of the patient. The values are somewhat higher for adult males than for females, and are considerably higher in general after adolescence. In adrenal cortical hyperfunction the urinary excretion of the 17-ketosteroids may be normal or increased. In general, excessive quantities are excreted in the presence of an adrenal cortical carcinoma, while in benign adrenal cortical tumors the urinary values may be normal. The large amounts excreted in cortical carcinoma are due essentially to an increase in the beta fractions. In adrenal cortical hyperplasia there is frequently a moderate increase in the urinary 17-ketosteroids. In summary, therefore, a normal urinary excretion of the 17-ketosteroids is not evidence against the diagnosis of adrenal cortical hyperfunction, since such values may be obtained in benign adrenal cortical tumors and in virilism or Cushing's syndrome without any overt adrenal cortical pathology. A marked increase in the urinary excretion of these compounds almost always indicates adrenal cortical carcinoma, while a moderate increase is observed in both carcinoma and hyperplasia.

The 11-oxy-ketosteroids are those compounds with an oxygen grouping on the 11th carbon atom. In a general way they parallel the urinary excretion of the 17-ketosteroids, but there are instances of adrenal cortical hyperfunction in which the urinary excretion of the

11-oxy compounds is increased while the values for the 17-ketosteroids remain within the normal limits.

The term "urinary glycocorticoids" refers to those compounds manufactured by the adrenal cortex which exercise an effect on carbohydrate metabolism. They parallel the urinary excretion of the 11-oxyketosteroids. They are generally excreted in large quantities in the urine of those patients who excrete excessive amounts of the neutral 17-ketosteroids. But here also there are not infrequent instances in which there is no parallel between the urinary excretion of the glycocorticoids and the 17-ketosteroids.

In adrenal cortical hyperfunction excessive quantities of estrogens or androgens may be excreted in the urine, as determined by biologic assay.

In the interpretation of the results of the urinary excretion of these compounds it must be borne in mind that the results are significant only if the compounds are excreted in abnormal amounts. Normal urinary values may not be used as an argument against the diagnosis of hyperadrenalcorticalism, although they rather point against the diagnosis of adrenal cortical carcinoma. The urinary presence of large quantities of these substances strongly favors the latter diagnosis, while a moderate increase would suggest hyperplasia but may also occur in carcinoma or even in the case of benign tumors.

Since the prognosis and treatment are so largely dependent on the underlying pathology, it is important to determine whether the patient has an adrenal cortical tumor or hyperplasia or primarily pituitary disease. Rarely, an abdominal tumor may be palpated: Not infrequently an adrenal mass can be identified by intravenous pyelography. Generally more definitive aid can be obtained by peri-renal insufflation. This method consists of the roentgenologic study of the abdomen after peri-renal insufflation with oxygen. By this technique the adrenals are well outlined and the presence of a tumor or enlargement is more readily demonstrable. Wilhelm recently suggested the use of laminography in peri-renal insufflation and found the combined technique superior to films made after simple peri-renal insufflation in delineating the normal adrenal gland and its lesser enlargements.

The treatment of adrenal cortical hyperfunction is determined in greater part by the nature of the underlying pathology. In general the therapeutic measures consist of the use of various hormonological agents

such as testosterone or estrogens, the use of x-ray treatment to the pituitary and adrenals, and finally surgical intervention.

Albright was the first to demonstrate the beneficent effects of large doses of testosterone. Following its use the patients became stronger, they developed a positive nitrogen balance, the osteoporosis and the hirsutism were lessened, and in general the patients were reported to show considerable improvement. Unfortunately, our experience has not been so satisfactory. All our patients were treated with testosterone before being subjected to more hazardous procedures. In no instance could we demonstrate any definite change, other than perhaps some decrease in the asthenia. Our results with estrogens have been equally discouraging.

Irradiation of the pituitary in instances of pituitary basophilism with or without associated adrenal cortical hyperplasia has its proponents. There are unquestionably well documented, although isolated, instances in which the results have been dramatic and curative. By far and large, however, this therapeutic measure has generally been unsuccessful. Again, all the patients in our series were subjected to pituitary irradiation before surgery was resorted to, without any success. However, because of the occasional good response and the great hazards attendant upon surgery, both testosterone and pituitary irradiation should be tried first. The results with x-ray treatment of the adrenals have been uniformly unsuccessful¹.

The surgical approach directed to the adrenals is a complicated and hazardous one, but if successfully executed results in cure. The greatest danger lies in the removal of a benign adrenal cortical tumor producing Cushing's syndrome. In these instances the contralateral adrenal is atrophic and the removal of the tumor results in a curious shock-like state in which the mortality rate is inordinately high. This shock is not that of the usual Addisonian crisis, in that it ensues directly after operation despite the pre- and postoperative administration of large amounts of adrenal cortical extracts and parenteral fluids. In addition, the blood electrolytes are normal in spite of the critical condition of the patient. Nor does the shock represent a hypoglycemic episode, since the blood sugar levels are generally well within the normal range. This postoperative state unquestionably represents the sudden deprivation of some adrenalcortical fraction or fractions as yet unidentified, which are vital to the body economy. In the presence of virilism alone—that is where

there are none of the metabolic disturbances characteristic of Cushing's syndrome—the removal of a benign adrenal cortical tumor is a fairly safe procedure. The difference in operative risk between this group and that with Cushing's syndrome is due to the fact that in the former the opposite adrenal is perfectly normal, and hence the removal of the tumor does not actually deprive the organism of any vital fractions.

When the adrenal cortical tumor is malignant its removal is somewhat less risky than when it is benign. This is particularly true when the tumorous growth has penetrated the capsule. These patients tend to survive the operative procedure in part because the tumor is not actually completely eradicable locally, and in part because distant metastatic spreads have already occurred in most instances. The local and distant metastases represent viable cortical tumor tissue which prevents the development of acute adrenal insufficiency. Unfortunately these patients eventually succumb to the malignant process, although they may show a dramatic regression of the symptoms for a short while after the removal of the primary tumor.

There is a great deal of difference of opinion concerning the advisability of operating on patients with adrenal cortical hyperfunction in whom the underlying pathology is that of bilateral adrenal cortical hyperplasia. The surgical procedures advocated in this group involve the removal of one hyperplastic gland, or the removal of one whole gland and half of the other, or the removal of half of each gland. The procedure employed in our clinic has been the removal of one of the hyperplastic adrenals, and our experience has been quite satisfactory, although the numbers are too small from which to draw any definite conclusions. The operation is not particularly hazardous although technically rather difficult since most of the patients are obese and the surgical approach difficult. The postoperative course is stormy during the first twenty-four to forty-eight hours, but we have had no fatalities to date. The therapeutic response has been good, with a considerable regression of the signs and symptoms.

The preoperative preparation and the postoperative care of the patients is of extreme importance. This applies particularly to those patients with benign adrenal cortical tumors, but is only slightly less important in patients with malignant cortical tumors or cortical hyperplasia. The preoperative preparation consists of the use of liberal quantities of whole adrenal cortical extract and the lipoid fraction now

commercially available and the administration of parenteral isotonic saline in 5 per cent glucose. These measures are instituted on the morning of the operation and continued throughout the operation and post-operative period until the patient is well out of danger. One must be on the alert for the development of certain therapeutic complications, especially peripheral and pulmonary edema. These complications are more likely to ensue following the excessive use of desoxycorticosterone than with whole adrenal cortical extract. In either event, if peripheral or pulmonary edema develops both the extract and the parenteral fluids must be discontinued temporarily.

COLITIS*

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COLITIS has been used loosely to cover all conditions of dysfunction of the bowel. This is erroneous. The term "colitis" specifically refers to inflammatory lesions of the colon. It does not include the various forms of bowel dysfunction in which there is no inflammation. It should be pointed out that while dysfunction often is manifested in inflammation of the bowel, not all dysfunction is associated with or caused by inflammation. It is suggested that the term "colitis" be reserved for only those lesions of the colon in which there is inflammation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of inflammatory lesions of the bowel involves a clear-cut understanding of the difference between bowel dysfunction, which is not associated with any pathological changes, and lesions of the colon, which are either specific or non-specific in character.

It has been shown by Bercovitz,^{1,2,3} in a series of studies on cellular exudates of bowel discharges, that the mucus or bowel evacuations from a healthy colon contain no significant cells. On the other hand, the presence of cells of various types, especially polymorphonuclear leukocytes, round cells and macrophages, is indicative of pathological changes, even though these may not be visualized through the sigmoidoscope or in roentgen-ray films made with contrast media.

The best way to obtain specimens for examination is to give three saline enemas to cleanse the bowel of fecal matter. The mucus or other material evacuated about one hour after the last enema is then examined. The mucus should be examined immediately after passage first on the warm stage for evidence of motile amebae, and then by means of Loeffler's methylene blue wet preparations for the study of cellular

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elements. The patient with simple bowel dysfunction has no cellular exudate.

Inflammatory lesions of the bowel which enter into the differential diagnosis of "colitis" may be classified as follows:

I SPECIFIC

Bacterial (Shigella group (bacillary dysentery), cholera, and other organisms whose role is not clearly understood, such as various streptococci and *Escherichia coli*)

Protozoan (*Endamoeba histolytica*, *Endolimax nana*, *Balantidium coli*, *Girardia lamblia* and *Plasmodium falciparum*)

Helminthic (*Schistosoma mansoni*, *S. japonicum*)

Virus Infections (*Lymphopathia venereum*)

II NON-SPECIFIC

Chronic Ulcerative Colitis (cause unknown)

Diverticulitis

Ileitis (regional, terminal ileo-colitis)

Nutritional Deficiencies

III OTHER CONDITIONS TO BE RULED OUT

Psychosomatic

Malignancy of the Gastrointestinal Tract

Gastric, gall bladder or pancreatic disease, and diseases of the genito-urinary tract

GENERAL MANAGEMENT OF COLITIS

The management of inflammatory disease of the bowel includes not only specific therapy, when indicated, but also treatment of the patient as a whole. The success of any program of therapy will depend upon the extent to which each of these is carried out.

In the general management of the colitis patient, psychosomatic factors and the nutritional state of the patient should be evaluated.

Since it is often impossible to state with certainty to what extent the psychogenic factors are responsible for the colitis and resulting bowel dysfunction, it is of the greatest importance that the patient and his problems be carefully evaluated and every effort made to establish a definite anatomical diagnosis. It is unfair to both the physician and the patient to make the diagnosis of psychoneurosis without prolonged painstaking investigations in order to establish the correct diagnosis. Consultations with other physicians, who have not seen the patient

previously and are therefore not too strongly aware of the psychoneurotic factors, are helpful.

The colitis patient cannot be treated casually or in a hurry. It may require weeks or months of observation before the true nature of the disease manifests itself. The physician must take time to understand his patient and win his confidence. It is only by carefully observing his patient, listening sympathetically to his story and encouraging him to release his worries and cares, that the physician can win his patient's confidence to be rewarded ultimately by being able to make a diagnosis. Often there are social aspects, intimate family and marital problems, financial difficulties, and even small worrisome matters, which are related to the problem, and it is a great comfort and benefit to the patient to know that the attending physician is concerned, understands and is anxious to help.

The physician should under no condition tell the patient that he is psychoneurotic, but rather should reassure him that his complaints are quite normal. It should be remembered that any patient who has diarrhea, pain in the abdomen, with loss of weight and strength over a period of time, is bound to become neurotic and distressed over points which would ordinarily be insignificant. Furthermore, the physician should be aware that the psychoneurotic manifestations of bowel disease are frequently the first indication that there is anything wrong with the patient.

Every patient with bowel dysfunction should be given proper treatment, even though the symptoms appear to be purely psychosomatic in origin. This is imperative, since the various types of bowel dysfunction are frequently the precursors of bowel diseases. Therefore, if the physician bears in mind that his patient with bowel dysfunction is a candidate for actual gastrointestinal pathology, including inflammatory changes and malignant degeneration, many of the late effects may be eliminated.

The general nutritional condition of the patient is the second important factor to be considered in the management of colitis. This includes careful evaluation of fluid balance, proteins, carbohydrates and vitamins. These apply not only to the acute dysenteries and diarrheas, but also to chronic conditions, especially chronic ulcerative colitis.

The therapeutic indications are for a minimum of 2500 cc. of fluids in 24 hours. This should be given by intravenous infusion for the first

day or two in cases of acute diarrhea. The use of 5 per cent glucose in normal saline is most acceptable, and in most instances 500 cc. of plasma should be given at least once during the day. To each infusion of 1000 cc. may be added 100 mg. thiamine chloride, 100 mg. niacinamide and 1000 mg. ascorbic acid. This program of fluid administration should be carried on simultaneously with specific therapeutic agents.

Whole blood transfusions are of great value both in patients with acute and chronic diarrhea, and in patients with inflammatory disease of the bowel, such as acute or chronic bacillary or amebic dysentery and chronic ulcerative colitis.

Dietary in the acute and chronic inflammatory diseases of the bowel has been a subject of great controversy in the past few years. For a long time it was the consensus that every consideration should be toward maintaining a non-irritating diet and to provide food which does not have any residue or roughage in order to put the bowel at rest and thus reduce the number of bowel movements in the day.

The patient with an inflammatory disease of the colon has bowel movements of blood, mucus and pus because of the inflammation, especially of the rectum and sigmoid, and not simply because of the food he may eat. Food taken into the stomach will provoke a defecation reflex as a purely physiological reaction. This is shown in cases in which ileostomy or colostomy has been performed. It is not the irritation caused by any single food, but the inflammation of the bowel which causes the diarrhea. This mechanism of the defecation reflex should be carefully explained to the patient so that he will not fear eating and will cease attributing every desire to evacuate the bowels to the foods taken into the stomach.

The dietary indications in acute and chronic inflammatory diseases of the bowel are for a full, balanced diet, particularly rich in proteins and vitamins. The foods should be prepared and served attractively, with every effort made to approach the normal diet. The practice of serving all foods in pureed form is unfortunate. Giving the patient food he can chew helps both psychologically and physiologically. More than ten years of experience in following this practice has proved it is without harm to the patient. Moreover, patients state that they feel better and have less abdominal distress when maintained on a liberal diet.

The only contraindications in diet are highly spiced foods and members of the cabbage and onion families. Food should be prepared simply,

well cooked and flavored to the patient's taste. It is best to give frequent small feedings, each containing an adequate amount of highly nutritious food.

Hydrochloric acid has been found of great value as a digestive aid. A dose of 30 minims in one-half of a glass of water after each meal is indicated. Other drugs, except as specifically indicated in the various infections, are generally contraindicated. Opiates give slight, but very temporary relief, and have the disadvantage of being habit-forming. Most patients state that while the opiates give some relief in the number of evacuations, there is distention, abdominal distress, and ultimately profuse movements which leave the patient weaker than if the drug were not given. Sedation with small dosages of barbiturates is indicated in highly nervous patients, and such preparations as syntronal, belladonna and bellergal seem to give relief and comfort at times.

Vitamin preparations are of value, and the selection should be based on potency and palatability. Parenteral injection is indicated wherever there is a question about absorption from the gastrointestinal tract. This is the method of choice during the acute stages.

Specific therapy, wherever indicated, will be considered under the various types of bowel inflammation.

BACILLARY DYSENTERY (COLITIS)

Bacillary dysentery (colitis) is an acute inflammatory disease of the large bowel caused by one of the Shigella group of organisms. The intensity of the infection and the clinical picture varies within wide limits, depending partly upon the virulence of the infecting organism and upon the resistance of the patient at the time of the infection.

The usual clinical picture is outstanding and characterized by the sudden onset of diarrhea with straining, tenesmus, blood, mucus and pus. The patient is toxic, feverish, and has bowel movements numbering 20, 30 or more a day. The patient is literally glued to the bedpan, and after great effort expels only a small amount of mucus and pus which stick to the bedpan.

On sigmoidoscopic examination, the bowel is found to be inflamed, necrotic, with definitely ragged ulcerations usually in the transverse axis of the bowel. Heavy, purulent, mucoid material is present, which on microscopic examination shows a heavy cellular exudate of polymorphonuclear leukocytes, denuded epithelial cells and macrophage cells

—all with ringed nuclei and with many toxic granules. It is possible to make a presumptive differential diagnosis between amebic and bacillary dysentery on the basis of cellular exudate studies. Cultural examinations made early in the disease directly from the ulceration will usually yield organisms of the *Shigella* group.

The therapeutic indications in bacillary dysentery (colitis) are two-fold: namely, specific to eradicate the causative *Shigella* organism, and general systemic to improve the general condition and comfort of the patient.

Specific therapy involves the use of one of the sulfonamide drugs. Sulfaguanidine has been shown to have a specific therapeutic action in bacillary dysentery; but sulfadiazine, used in various parts of the world where sulfaguanidine was not available, was found to have an equally specific action. In fact, in the author's experience in India, sulfadiazine became the drug of choice, and the response noted was as dramatic as that obtained with sulfaguanidine and equally as specific.

The recommended dosage of sulfaguanidine in the treatment of acute bacillary dysentery is 3 or 4 grams initially, followed by 2 grams every three hours day and night for the first 24 hours or until the bowel movements become less frequent, the straining and tenesmus are relieved, and there is a passage of fecal material. After the first 24 hours, the midnight dose may be omitted. It has been found that by the end of the second day the patient will have made sufficient progress to warrant reduction of the dose to 1 gram every four hours. This dosage should be continued for at least four or five days even though the patient appears to be symptom free.

Most noteworthy in the author's wartime experience with bacillary dysentery was the fact that patients made dramatic recoveries, as evident from symptomatological improvement and sigmoidoscopic findings, but did not have the tendency to develop chronic ulcerative colitis; as previously seen so frequently after bacillary dysentery infection. It was found that after a week of sulfaguanidine or sulfadiazine, proctoscopic examination revealed an entirely normal bowel mucosa with negative cellular exudate on study of the bowel discharges.

The general systemic approach to the treatment of bacillary dysentery is equally as important as the specific chemotherapy. The patient should be given by intravenous infusions 5 per cent glucose in normal saline. To each 1000 cc. may be added 100 mg. thiamine chloride, 100

mg. niacinamide and 1000 mg. ascorbic acid. A minimum of 2000 cc. should be given intravenously until the patient is able to take adequate fluids by mouth. In addition, 500 cc. of plasma should be given intravenously during the first 24 hours, making a total of 2500 cc. of fluid injected the first day of treatment. Sedatives of the phenobarbital group may be administered, but the opiates, including paregoric, tincture of opium, are not only unnecessary but contraindicated. In most instances the patients appear more toxic and have more abdominal distress after the opiates. The response to sulfaguanidine or sulfadiazine is so prompt and effective that the opiates are unnecessary.

The diet should be high in proteins and vitamins, and the patient should be encouraged to eat solid foods and take fluids by mouth at the earliest possible moment. This is most important, since the patient with profuse diarrhea, is losing proteins and vitamins which must be replaced. If it is remembered that the bowel movements are caused by the inflammation of the sigmoid and colon, and not by the food the patient eats, many patients will be saved from starvation, which often results because proteins and vitamins are not replenished as they are lost.

AMEBIC DYSENTERY (COLITIS)

Amebic colitis is caused by an infection with *Endamoeba histolytica*. In its simplest form, there is typical ulceration with a normal mucosa surrounding. The amebic colitis may be either acute or chronic. In the acute stages the symptom picture is quite characteristic, with diarrhea amounting to 4, 6 or 8 bowel movements in 24 hours and with no straining nor tenesmus. The patient is only moderately ill, and is not as toxic as in bacillary dysentery; generally there is no fever. The bowel movements are usually copious and may or may not contain visible mucus and blood.

In those cases in which the infection has persisted for a considerable length of time and has become chronic, the clinical picture varies within very wide limits, and it is quite impossible to describe a so-called typical or classic picture of chronic amebiasis. There may be alternating diarrhea and constipation, some flatulence with more or less gas, and vague abdominal pains are frequently present which makes the patient conscious of his abdomen. Constipation is not an infrequent symptom of amebiasis; in fact, there are a great many patients who claim that they have never had an attack of diarrhea but have suffered only from con-

stipation.

The diagnosis depends upon finding the typical forms of *E. histolytica* in specimens of the stool or other bowel discharges. In making the diagnosis, the various concentration tests should be used, especially the Faust centrifugal flotation with zinc sulphate or Otto's modification of the technique. If these methods fail to reveal amebae, then the patient should be given saline enemas, and freshly passed mucus examined for amebae. The patient also may be given a dosage of Epsom salts, and the stools passed in the laboratory so that they can be examined fresh and warm.

In evaluating the mucus specimens, it should be remembered that there are many cells which come down in the bowel discharges and which may be confused with *E. histolytica*. These are most frequently macrophages, polymorphonuclear leukocytes, epithelial cells and plasma cells, and cause confusion especially in freshly passed, unstained material. Cells of tissue origin should be carefully identified to avoid mistaking them for *E. histolytica*. Ofttimes chronic ulcerative colitis, carcinoma of the colon, especially the rectum or sigmoid, and lympho-granuloma are treated as chronic amebiasis and the real nature of the condition missed until it is too late to help. To avoid such instances of mistaken diagnosis, the findings should be confirmed by those qualified in the differential diagnosis, especially by fixed stained preparations.

It should be pointed out that there are cases of chronic amebiasis of long duration in which it may not be possible to demonstrate forms of *E. histolytica* in the stools. This is particularly true of some of the complications of amebiasis, such as amebic granuloma, amebic hepatitis and amebic typhilitis. In these instances the diagnosis must be made on the basis of clinical history, physical findings and the response to specific therapy with emetine.

Sigmoidoscopic examination may show only a moderate degree of atrophy of the bowel mucosa; occasionally, there may be typical amebic ulcerations; or there may even be a normal rectum and sigmoid with the lesions being present higher up in the bowel. There may be secondary bacterial infection of the bowel such as in bacillary dysentery, in which case the sigmoidoscopic picture is that of the acute process.

The complications of amebiasis have been outlined by Bercovitz⁴ and include secondary bacterial infection of the amebic ulcerations, perforation of the bowel, amebic hepatitis with or without abscess for-

mation, amebic granulomata especially of the sigmoid or cecum, amebic appendicitis, typhilitis, and the more uncommon complications of amebic abscess of the spleen following perforation of the splenic flexure of the colon, and amebic abscess of the brain and lungs. Amebic abscess of the prostate has been seen.

The therapeutic approach to the problem of amebic colitis and its complications must include a careful evaluation of the patient as a whole and treatment of the patient, and not only his parasites. It should be remembered that in more than 90 per cent of the cases of acute amebiasis studied there is some secondary bacterial infection of the bowel, and in about 50 per cent there is evidence of amebic hepatitis. Thus every patient should be carefully studied for evidences of secondary infection, such as cellular exudates in the bowel discharges in amebiasis, liver tenderness, thickening of the bowel over the cecum or descending colon and sigmoid area.

Table I is taken from a recent article by Bercovitz⁴ and summarizes the drugs most commonly used in therapy of amebiasis.

Emetine is the most valuable drug in amebiasis, and is indicated in both the acute and chronic stages of infection, as well as in complications. Where the infection is of long duration the parasites tend to get deep into the tissues, and in such cases emetine in addition to oral medication is indicated. In cases of failure, it is not a question of the parasites being "emetine-fast," but rather a problem of secondary bacterial infection which makes it impossible for the drug to reach the parasites. The same applies to other drugs used in the treatment of amebiasis.

On the basis of the author's experience, the following course of therapy has been found most acceptable and results in complete eradication of the infection. A course of emetine is given simultaneously with a course of sulfadiazine for seven days. This is then followed by a course of 200 tablets of diodoquin. The sulfadiazine may then be repeated once and followed again by the diodoquin. Diodoquin is the drug of choice in that it causes the least amount of irritation with highest efficiency. The most important point to remember is that the dosage must be adequate. Therefore, a dosage of 200 tablets given in doses of 4 tablets four times daily (16 tablets for the total daily dosage) is used. Under this program there have been no failures.

TABLE I.—TREATMENT OF AMEBIC DYSENTERY†

<i>Drug</i>	<i>Single Dose</i>	<i>Number of Doses Daily</i>	<i>Total Daily Dosage</i>	<i>Total Dosage of Single Course of Treatment</i>	<i>Indications</i>
Emetine hydro-chloride*	½ gr. (0.032 Gm.) Subcutaneously	2 (a.m. and p.m.)	1 gr. (0.0065 Gm.)	7 gr. (0.455 Gm.)	Acute and chronic amebiasis, amebic granuloma, hepatitis, typhilitis perforations
Diodoquin Tablets of 3.2 gr.	4 tablets	4 (four times a day after food and bedtime)	16 tablets (3.84 Gm.)	200 tablets (64.00 Gm.)	Acute and chronic amebiasis with trophozoites and cysts of <i>E. histolytica</i>
Chiniofon Tablets of 0.25 Gm. each.	2-3 tablets	3 (three times a day after food)	6-9 tablets (1.5-2.25 Gm.)	100 tablets (2.50 Gm.)	Chronic amebiasis, cyst passers
Vioform Tablets of 0.25 Gm. each.	3 tablets	3 (three times a day after food)	9 tablets (2.25 Gm.)	100 tablets (25.0 Gm.)	Acute and chronic amebiasis with cysts of <i>E. histolytica</i>
Carbarsone† Capsules of 0.25 Gm. each	1 capsule	2 (a.m. and p.m.)	2 capsules (0.5 Gm.)	20 capsules (5.0 Gm.)	Chronic amebiasis, with cysts

* Myocardial poison—give subcutaneously only. Never to be given by intravenous or intramuscular injection. Blood pressure and pulse should be checked before each injection. Patient should be kept at bed rest if possible.

† Carbarsone is an arsenical and should not be used in any cases suspected of liver damage, such as amebic hepatitis.

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CHRONIC ULCERATIVE COLITIS

Etiology: The etiology of chronic ulcerative colitis is still obscure, despite the large number of studies made. An extensive analytical review of the literature on the etiology of chronic ulcerative colitis published by Ginsberg and Ivy,⁵ revealed that there is no single etiological factor responsible for all cases.

Chronic ulcerative colitis as a disease entity may follow many disease conditions. Amebic and bacillary dysentery have been followed by this disease; indeed, there are certain cases in which these infections might seem to be the precipitating agents. Undoubtedly emotional and psychogenic factors are concerned, but it is difficult to attribute sole cause to them. There have been many instances in which great emotional and psychological upsets have been attended by attacks of diarrhea with dysfunction of the bowel, and in such instances when the condition persists over a long period of time, it is conceivable that permanent bowel damage may occur.

Although the causative agent in chronic ulcerative colitis has not been established, it is essential to conduct prolonged and intensive investigation of all the possible factors and to give the patient the benefit of the various specific therapeutic measures available.

Complete investigation of cases of chronic ulcerative colitis involves repeated careful microscopic examination of exudates both before and after saline enemas for amebae, cellular exudate studies with Loeffler's methylene blue, sigmoidoscopy to rule out malignancy, cultures of mucus and bowel discharges for pathogenic microbes, and finally, roentgen-ray examination of the colon with the barium colon enema. In addition to these, it is essential to make gastric analyses and to determine plasma ascorbic acid, prothrombin clotting time, plasma proteins and glucose tolerance. These studies will in many instances give the therapeutic indications for the patient as a whole.

Treatment: Treatment of chronic ulcerative colitis consists of two parts, much in the same way as that of treating other forms of colitis: (1) treatment of the patient as a whole, and (2) treatment directed against the specific infection of the bowel.

As previously stated, psychological and emotional factors must be considered in the management of chronic ulcerative colitis as they are in other forms of colitis. The patient who has chronic diarrhea, ab-

dominal pains, anorexia, nausea, and the general debility which goes with the disease, is also affected psychologically and becomes emotionally unstable.

Patients with chronic ulcerative colitis must be understood to be helped. It is imperative that under no circumstances are they made to feel that they are mental cases. They should be encouraged and repeatedly told that they will be cured and be normal again. Every sign of encouragement should be stressed, even if it is temporary, and the physician should never display his discouragement. The family physician must employ practical psychotherapy. The patient should be given time to talk and ask questions, each of which should be answered whenever possible.

In addition to creating mental rest and peace of mind in his chronic ulcerative colitis patient, the physician should employ physical rest and relaxation. Narcotics and habit-forming drugs should be avoided. Opium has been a favorite drug to reduce bowel movements, but it is ineffective except as a temporary measure and has the disadvantage of becoming habit-forming. Many a patient with chronic ulcerative colitis has become an addict because of the unfortunate use of forms of opium. This practice should be eliminated. The barbiturates are much more satisfactory, but they, too, may be habit-forming. No matter what drug is used for sedation, it is important not to continue it for too long a period.

Nutrition and Diet: Maintenance of proper nutrition of the patient is the major problem confronting the physician treating a case of chronic ulcerative colitis. It must not be forgotten that the patient has a diarrhea and moves his bowels with blood, mucus and pus because he has an inflammation of the bowel, especially of the recto-sigmoid area, and that he does not move his bowels because of the food taken into his mouth and swallowed which may evoke a defecation reflex.

The physician should be prepared to dispel the erroneous belief of many patients that because they have diarrhea following any single meal it is to be attributed to the food consumed. This is important to ward off the ill effects of elimination of essential foods from the diet, when there is no just cause other than the patient feels it is the food he eats that causes the diarrhea.

The practice of giving perfectly bland diets to remove all roughage from the colon has not cured the inflammatory lesions of chronic ulcera-

tive colitis. In fact, it has been noted that even when an ileostomy has been performed and the colon put entirely at rest in so far as fecal matter is concerned, the patient still passes blood, mucus and pus from the rectum because of the inflammation present.

There is ample evidence to show that patients with chronic ulcerative colitis are soon depleted of their reserves of proteins, vitamins and other essentials for nutrition and tissue repair. The therapeutic indications, therefore, are for an adequate, liberal diet with enough proteins, carbohydrates and vitamins to replenish the losses suffered from the disease and the diarrhea. It should be remembered also that the patient with chronic ulcerative colitis does not absorb adequate amounts of food even though it is not possible to demonstrate roentgenologically any lesions of the small bowel. Thus the nutritive content of his diet must be increased to replace his losses and to make up for the poor absorption of whatever food he does take in. It has been proved by experience that patients who take an adequate amount of food, not only feel better and are stronger, but they do not have as much abdominal distress.

The diet in chronic ulcerative colitis cases should include adequate amounts of proteins, especially meats. These should be dictated by the taste and desires of the patient. Beef steaks, roasts, chopped meats, boiled or broiled, and tastily served are excellent sources of essential proteins, and should form the basis of any chronic ulcerative colitis diet. Vegetables and fruits in keeping with the patient's likes and dislikes should also be served.

All food should be properly prepared and special attention should be given to serve the menu attractively, to stimulate the patient's appetite and desire for food. It has been a common experience that a patient will tolerate and eat many vegetables which are cooked and served in natural form, but will become nauseated at the sight of puréed spinach with butter, or other puréed and strained vegetables. Puréed vegetables may be disguised by using them in creamed soups, in which form they may be enjoyed; but it should be mentioned that the concept of serving puréed vegetables to prevent roughage and thus reduce bowel movements is without scientific foundation. On the contrary, experience has shown that the patient who eats an adequate amount of meats and vegetables does better and has less pain. The same applies to simple salads such as lettuce and well-ripened tomatoes, or fruit juices such as orange and grapefruit juice. The use of a whole orange or whole

grapefruit is to be encouraged, and in many instances it has been found that the serving of grapefruit revived the appetite of the patient and stimulated his normal eating pattern.

The rule, then, in the nutritional management of chronic ulcerative colitis is the administration of high protein, high carbohydrate, high vitamin diets with intermediate feedings as often as possible, and every effort made to avoid starvation with further depletion of the body tissues.

Intravenous Fluids: Parenteral administration of body fluids, proteins and vitamins is of indisputable value, and every patient should be given the benefit of such treatment. Intravenous infusions of 500 cc. of plasma once or even twice daily are indicated in severe cases. To each infusion may be added 100 mg. thiamine chloride, 100 mg. niacinamide and 1000 mg. ascorbic acid. Blood transfusions in amounts of 250 to 500 cc. at frequent intervals are invaluable. In severe cases the use of blood and plasma daily or every other day may be absolutely necessary to save life. It has been found that even chronic cases who are not moribund, but seem to be holding their own and maintaining a stationary course in their disease, may be helped considerably by parenteral administrations.

Intravenous infusions of glucose in normal saline are also indicated to maintain fluid balance in the patient. Vitamins in the same concentrations as in plasma infusions may be added to the glucose infusion. The total amount of fluid intake in cases of chronic ulcerative colitis should be a minimum of 2000 cc. daily.

The administration of parenteral injections should be determined by the physician after careful evaluation of the patient with respect to the number of bowel movements, the quantity of material passed, the nature of the evacuations, the diet and the amount of food consumed by the patient. Ofttimes despite the fact that laboratory reports indicate seemingly adequate numbers of erythrocytes or plasma proteins, there may be need for supplementary parenteral administrations when these factors are considered.

Specific Chemotherapy: The use of specific drugs in chronic ulcerative colitis has been disappointing up until the present time. This was adequately brought out in the symposium on the use of the sulfonamides in gastrointestinal diseases held by the American Gastroenterological Association and reported recently.⁶ Neither the sulfonamides, nor

penicillin, nor streptomycin has been effective in bringing about cures. This has been the experience of all those who have followed their cases for sufficient time to make careful evaluation of their results.

The sulfonamides have been used extensively. It is true that in many instances there have been what seemed to be dramatic effects following the administration of the various forms of sulfonamides, but follow-up of these patients revealed no permanent "cures." However, the temporary beneficial effects noted would warrant the continued use of the sulfonamides provided the patient is carefully observed for untoward effects of these drugs and their use is not prolonged. It should be noted that merely changing the bacterial flora of the bowel contents is not sufficient to cure a case of chronic ulcerative colitis. The causal relationship of any single microorganism to chronic ulcerative colitis has not been demonstrated adequately as yet.

Penicillin and streptomycin have given disappointing results. Some patients receiving streptomycin seem to become worse. In my experience penicillin has not given even the temporary beneficial effects sometimes seen following the administration of the sulfonamides.

Evaluation of any Form of Therapy in Chronic Ulcerative Colitis: The evaluation of any form of therapy in chronic ulcerative colitis must be made with caution. Only after a large number of patients have been studied and followed over a period of not less than five years can any statement be made regarding the value of a particular form of therapy. The need for the use of placebo therapy prior to the actual medication is of the utmost importance.

Certain criteria for evaluation of therapeutic results are necessary and the minimum standards must be rigidly followed. The criteria for cure in this disease are divided into two main groups; namely the clinical symptomatology and the objective findings of the laboratory and sigmoidoscopic examination.

Clinical evaluation of response to therapy is always concerned with the psychological response of the patient to any new medication or new system of therapy. The patient's statement concerning the number of bowel movements, the character of the stools, should be carefully weighed and studied, until they are formed, normal in size and shape, and without blood, mucus, or pus present.

The matter of sphincter control is of the greatest importance, and also the number of night evacuations. Abdominal cramps, pains and

gas should disappear. Improvement in the general well-being of the patient, as well as in his appetite and weight are other factors to be considered.

Laboratory studies should reveal a reduction in the sedimentation rate and clearing of the cellular exudates of the bowel discharges. A normal sedimentation rate and bowel discharges without cells are the fundamental objective basis for a statement of cure or improvement in any case.

Sigmoidoscopy is of value but the personal enthusiasm of the examining physician must be considered. However, if there is loss of ulcerations, clearing of the submucous hemorrhagic areas which are usually pin-point or larger in size, reduction in the edema, inflammation and thickening of the bowel mucosa, and the bowel becomes non-friable and will not bleed at the slightest contact with the sigmoidoscope when it is passed, then there is justification for an estimation of a cure. It should be pointed out that restoration of tone to the mucosa so that it is not friable is one of the last things to occur, and with it there is simultaneously a drop in the sedimentation rate and clinical improvement in the patient.

These standards represent the irreducible minimum for therapeutic evaluation in chronic ulcerative colitis. Not only must the patient be brought to this point to consider him cured, but he must remain in this condition for a minimum of five years. Otherwise it is impossible to state with certainty that the treatment was not given just at the time of a spontaneous remission, for such remissions have been observed up to five years.

Surgery in Chronic Ulcerative Colitis: The surgical indications in chronic ulcerative colitis have been stated clearly by Cave⁷ and others. The more frequent use of ileostomy has been avoided because until the present time, it has been impossible to point to any considerable series of cases, in which it has been possible to reestablish the continuity of the bowel and return the patient to a normal bowel status. In most instances permanent ileostomy with its associated inconvenience has been a stumbling block. Patients therefore have been carried on a medical regime in the vain hope of reaching a period of remission which will be prolonged and that a form of "cure" will be effected.

Such practice has in most instances resulted in the patient's becoming so weak and so depleted that when finally ileostomy was considered,

the patient was in such poor condition that the surgical mortality of the operation is far out of proportion to what it should be from a purely technical standpoint. Furthermore, by the time ileostomy is considered, permanent damage to the bowel has taken place, and the pathological changes occurring may be irreversible so that the ileostomy becomes permanent with no chance for recovery of normal bowel function.

It is too early at this time, and the number of cases is too small, to predict what the end results will be of experiments now in progress in which active therapy has been undertaken of the distal loop of the bowel following ileostomy. The results observed at this time are a marked improvement in the well-being of the patient, a decline in the sedimentation rate, and improvement in the objective appearance of the bowel wall. Further reports on progress will be forthcoming.

It may be that for the benefit of the patient, ileostomy will have to be performed earlier so that active therapy can be instituted and it may be possible to reestablish continuity of the bowel in the future after healing is complete. If, however, the delay is too long and the pathological changes have become irreversible, then no means of therapy will cause healing.

Prognosis and Complications: The prognosis of chronic ulcerative colitis should always be guarded because of the complications which generally occur. These have been outlined by Ricketts and Palmer.⁸ Under no circumstances is the true prognosis to be communicated to the patient or his immediate family. At all times the physician should hold out hope for eventual cure, and never display even the slightest doubt of the future lest the patient lose hope, quit fighting and die. There are thousands of cases of chronic ulcerative colitis who have become useful citizens and are performing useful functions in society even though they do not represent "cures."

The attending physician should be alert to such complications as perforations of the bowel wall. These may be minute, and as a rule are pin-point in character. They may result from the passage of infectious agents through the lymphatics to lodge in the bowel wall and cause a local area of peritoneal irritation with symptoms which point to a mild, more or less localized peritonitis.

The therapeutic indications in these cases is absolute rest in bed, the administration of one of the sulfonamides, preferably sulfadiazine, fluids by vein, and in cases where it is comforting, an ice bag.

In some instances the perforations may become larger, and actual abscesses may form along the bowel wall. These may become localized and well walled off, and under these conditions, it is better to treat the patient conservatively. If the bowel wall is so fragile that it has perforated spontaneously, the handling involved in finding the abscess and other manipulations may cause the death of the patient. Under these circumstances, there is no single surgical procedure which will cure the case, and as a rule other perforations are likely to occur. If an abscess becomes definitely localized and seems to be near to the abdominal wall, simple drainage may be considered, but even this is of great danger to the patient.

Stricture of the bowel is another complication which commonly follows a prolonged case of chronic ulcerative colitis. This may be single in the rectum or there may be multiple strictures in various parts of the bowel. When it is known that a patient has developed one or more strictures of the bowel, great caution must be observed to maintain the feces in a liquid state. If the patient is allowed to have a solid fecal mass, obstruction of the bowel will develop, which is most difficult to relieve.

It is possible to maintain a patient in good nutritional state for a period of years with two or three mushy bowel movements daily. This may be accomplished by means of carefully regulated dosages of milk of magnesia or sodium sulfate. Castor oil is contraindicated because of its constipating effect. One patient was thus maintained for eight years.

When roentgen-ray examinations of patients suspected of having bowel strictures are made, the roentgenologist should be informed so that he can use proper mixtures of barium and institute measures for elimination of the barium after the examination in order to avoid intestinal obstruction.

Carcinoma of the large bowel following chronic ulcerative colitis does occur, and has been variously reported by Cave,⁹ and Ricketts and Palmer⁸ and others. It would be expected that following a prolonged irritative lesion of the bowel, the incidence of cancer would be higher. On the other hand, hyperplastic changes of the bowel mucosa with polyp and pseudopolypoid changes are frequently observed in varying degree. In many instances, the entire bowel wall is involved in these changes, the process extending from the rectum to the cecum.

When this occurs, it is impossible to look forward to cure of the patient by ordinary medical measures. Such changes do not seem to progress into cancerous degenerations any more frequently than others. In a review of the available literature by Page and Bercovitz¹⁰ it was found that among a total of 1,467 cases of chronic ulcerative colitis reported with statistics on its association with carcinoma of the colon, only 28 developed carcinoma of the colon—an average incidence of 1.9 per cent. In this connection, Swinton and Warren (referred to by Page and Bercovitz¹⁰) stated that they have never observed progression of the polypoid changes associated with ulcerative colitis to a malignant stage.

HELMINTHIC COLITIS AND LYMPHOGRANULOMA VENEREUM

Helminthic colitis and lymphogranuloma venereum are dealt with briefly because they are relatively rare.

Infections with helminths, such as the various forms of *Schistosoma*, may be diagnosed first by consideration of the geographical location from which the patient has come, and then by careful studies of the stool for evidence of the organisms causing the infection. The specific diagnostic methods are discussed in textbooks of tropical medicine and parasitology, and more recently in publications coming from the U. S. Army Commission on Schistosomiasis. Treatment of infections with one of the forms of *Schistosoma* is by means of the antimony compounds, preferably fuadin.

Lymphogranuloma venereum is a specific virus infection which invades the lower bowel. It is more common in the female, but occurs also in males, especially after irregular sexual practices such as sodomy. In such cases there is usually a history of diarrhea, but on careful questioning it is revealed that the patient passes blood, mucus and pus from the rectum without any reference to the bowel movements; in fact, the patient who has had the disease for any length of time may actually be constipated as a result of the stricture which usually complicates the picture. The diagnosis is usually confirmed by proctoscopic examination, first by digital examination with notation of the stricture of the rectum within reach of the examining finger and the widely gaping anus from which there is a copious discharge of sanguinous pus and mucus. The mucosa is granular with innumerable tiny nodules, giving the finger the feel as though it were passed into a "bag of beans." The Frei test is positive.

Therapy of lymphogranuloma venereum of the rectum includes administration of the sulfonamides, especially sulfathiazole. If the stricture causes obstruction to the bowel, colostomy may have to be performed.

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PSYCHOLOGICAL ASPECTS OF OBESITY*

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A CLINICIAN of the last century divided obesity into three stages, known respectively as the enviable, the comical, and the pitiable. This is unusual language for medical classification. It illustrates well the peculiar place which obesity occupies in medicine. Obesity is not an illness, nor is it a malformation. It is here included in a program on disorders of metabolism and the endocrine glands. To a large extent this association must be considered as an expression of conformity with traditional concepts concerning the etiology of obesity. Recent studies embodying clinical as well as experimental work, bring little if any support to the view that obesity is caused by primary metabolic or endocrine disturbances; although it may happen, of course, that a person suffering from a true endocrine disorder is also obese. For those rare cases in which there is a localized organic lesion the disturbance seems to lie in central nervous regulatory mechanisms. For the great majority of fat people there is no uncontested evidence of any specific physiologic disturbance that could be regarded as the cause of obesity.

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Address before the Twentieth Graduate Fortnight, The New York Academy of Medicine, October 7, 1947.

Yet there are few conditions which cause such a distortion of the body and make a person as conspicuous as does obesity. All gradation exists and the border between the normal state of blooming good health and the abnormal state of disfiguring obesity is not at all distinct. Obesity becomes a medical problem in a strict sense only when it interferes with the well-being and efficiency of a person. Frequently it is a serious hazard to health when it is combined with other disorders such as diabetes, hypertension, orthopedic and cardiac conditions, to mention just a few. I do not wish to enumerate the many associations and interactions between obesity and other clinical disorders. Without complications obesity per se becomes a physical encumbrance only in its more extreme forms.

It has been said that there are few bodily conditions that cause quite as much unhappiness and misery as the unlovely state of corpulence. The suffering of the obese person is of a different order from that in other physical ills. It is not experienced as pain or bodily discomfort, but in a person's relationship to his fellow men. In this sense obesity belongs to the group of social and psychological disorders.

This fact that obesity becomes abnormal through its social connotations is well illustrated by the different prestige value which it carries with different people and at different historical times. With our present day attitude, for instance, it would be difficult to consider any stage of obesity as enviable. Western culture on the whole has ridiculed and despised fatness. Ancient Cretan mosaics depict women of great slimness with wasp-waists. Little wonder that the classical Greeks, their cultural successors, credited them with the knowledge of the "ideal drug"—a drug which would keep a person slim however much he ate.¹ According to an old source,² "Roman mothers, during the Empire, starved their daughters to make them slender as rushes and eligible in the marriage market."

On the other hand (I quote from the same source), "The Tunisians have a curious custom of fattening up their young ladies for marriage. A girl, after she is betrothed, is cooped up in a small room. The food used for this custom, worthy of barbarians, is a seed, which is of an extraordinary fattening quality; and Mr. Mungo Park tells of African mothers who cram meat down the throats of their daughters, that they may please the princes who range the great desert."

"We learn from Erasmus that the Gordii carried their admiration

so far as to advance him to the throne who was the fattest and most corpulent. And Bernier informs us that the Emperor of Mogul is annually weighed upon his birthday; when, if it appears that since his former weighing, he has made any considerable acquisition of flesh, it is matter of public rejoicings throughout his whole dominions."

These are just a few examples of extremes in evaluating obesity as a social asset or as liability, and they are partly based on hearsay tales of old travellers. Modern anthropologists have confirmed the existence of fattening houses in some African tribes, and that being fat may convey high prestige on certain people or professions. No systematic study has been made, as far as I know, of the question under what cultural conditions obesity adds to the repute of a person and under what circumstances it becomes a humiliating burden. It seems to be uncommon for obesity to be considered without special emotional significance or with indifference.

Even in our Western culture, with its general low esteem for fatness, variations in the evaluation of obesity occur as the beauty ideal changes. It is little more than a generation ago that an eminent French physician complained that "there can be no doubt that in order to have '*un décolleté impressionnant*' each woman considers herself duty bound to be fat around the neck, the shoulders and the arms. But it is just these places where fat accumulates with the greatest difficulty. One can, therefore, be sure that the abdomen, hips, thighs and lower extremities of a woman with well padded beautiful neck and shoulders, are in a state of hopeless adiposity. . . . As to treatment, she cannot achieve a reduction of the waistline, for which she clamors, without sacrificing, in her spirit, the upper parts of the body. It is a true sacrifice to the fashionable demands. . . . Thus one finds esthetic and social factors which are active enough to make women persist in being obese!"

This statement sounds so alien to us and as though from a different era that one has to look twice at the title page of the book from which the paragraph was taken, to make sure that it was published in Paris in 1911.³

Even at the same time, and I am speaking now of contemporary observations in New York City, a wide range exists in the emotional appraisal of obesity. Opinions vary all the way from the sophisticated remarks of Ogden Nash that "Some ladies smoke too much and some ladies drink too much and some ladies pray too much, but all ladies

think that they weigh too much,"—to the undisputable dictum of the mother of a fat boy that her family thinks the bigger he is the better he is!

These remarks on the wide range of social and emotional evaluation of obesity are intended as a background for the topic of the evening. If we speak of psychological aspects of obesity it is well to remember that the remarks apply only within the cultural and social setting in which observations have been made, and only to that fraction of the large number of fat people who come for treatment.

I shall discuss the problem from three different angles, namely, (1) the psychological aspects of being obese, (2) the psychological aspects of becoming obese, and (3) the psychological aspects of treatment. This third section will also deal with the psychological attitude of the physician in regard to the diagnosis and treatment of obesity.

PSYCHOLOGICAL ASPECTS OF BEING OBESE

A vivid description of the mental suffering of fatness was given by Banting in his famous "Letter on Corpulence, Addressed to the Public," published in 1863.⁴ He complains: "No man laboring under obesity can be quite insensible to the sneers and remarks of the cruel and injudicious in public assemblies, public vehicles, or the ordinary street traffic; nor to the annoyance of finding no adequate space in a public assembly if he should seek amusement or need refreshment, and therefore he naturally keeps away as much as possible from places where he is likely to be made the object of the taunts and remarks of others."

Since Banting's time obesity has vastly increased in its negative rating as an object of ridicule and humiliation. This is particularly true for young obese people. They feel more or less excluded from the activities of their age group and thus fail to develop interests and social skills necessary for success and happiness in adult life. The fear of embarrassment, of making a spectacle of themselves by exposing their unshapely figure, is so great that many obese young people become withdrawn and seclusive. They give up whatever sport and physical activities they had previously enjoyed; then they avoid larger groups and finally they even stay away from friends in order not to embarrass them, as they say, by their ungainly company. The preoccupation with weight and appearance may become so grave that it overshadows all other feelings and actions. Everything is experienced in terms of

"weight" and "figure." People are classified into fat and non-fat with a feeling of contempt and hatred for the fat ones and of envy and hopeless inferiority in relation to the slender ones. Many of the personality features of obese people, their shyness and over-sensitivity, their easy discouragement in the face of difficulties or when confronted with the slightest rejection, their tendency to depressions and their phlegmatic manner may be considered sequels to their constant concern with the impression they make on account of being obese—at least it might appear so.

The practical consequences of this preoccupation with their appearance are also serious. The young fat girl who feels unattractive has little prospect of getting married, particularly if she is so convinced of being rated only according to her size that she will not even permit herself to become interested in men. For many young people the fact of being fat stands like an unsurmountable obstruction in the road toward a cherished professional goal. Again I wish to add, at least it appears so.

There are, on the other hand, many fat people who deny any difficulties in living on account of their obesity. They are cheerful and unconcerned, easy going and friendly with everybody. They seem to confirm the popular opinion that a fat man is a jovial good fellow. There may be fat people amongst us who really are content and unconcerned. They are not likely to come to medical attention, at least not for the treatment of obesity. In those happy-go-lucky fat people whom I have had the opportunity to observe, the joviality and often boisterous cheerfulness was nothing but a thin veneer put on for the benefit of the public, a compensatory defense against underlying feelings of unhappiness and futility.

The really puzzling aspect of the psychology of obese people who blame all their misery and failures in life on "being fat," is their seeming unwillingness or inability to do something about it. Ordinarily, if one recognizes the source of one's suffering, one will bend every effort to remove it. Not so the obese person. On the contrary, their very reactions to being fat contain all the elements which go toward making the condition progressively worse. If one learns to understand fat people more intimately, it gradually appears that their tremendous size, which they so loudly bemoan, is not without a positive emotional meaning for them. This is more easily recognized when dealing with obese children who say quite frankly "I would want to lose weight

but I do not want to be skinny." Usually their mothers share the anxiety about losing weight. It seems that in the insecure and unstable relations to the surroundings physical size and bulkiness convey a feeling of strength, safety and power to the timid fat child. The heavy layers of fat seem to act as protective walls against an outer world which the fat person often experiences as unfriendly and threatening. Sometimes the very unattractiveness of obesity serves a definite emotional purpose. It offers a seemingly obvious reason for avoiding situations which might provoke fear and anxiety. Many fat young girls, though outwardly very concerned about not getting married, nevertheless persist in remaining fat because it is a protection against men and sex and the responsibilities of adult womanhood which they dread even more than the disgrace of being fat.

Such an ambivalent attitude towards themselves and their condition can be recognized in many psychological reactions of obese people. The more familiar one becomes with their problems the less clear-cut are the issues. What on first impression looks like an understandable reaction to being fat reveals itself as intimately interwoven with the emotional problems of becoming obese. The withdrawal from all social contacts which fat people so readily explain as due to their *obesity* is usually quite out of proportion; and it often precedes or coincides with the development of obesity. I mentioned before the low prestige value of obesity in our society. This unfriendly attitude of the environment, however, is really nothing in comparison with the contempt and self-hatred that many fat people express towards themselves. There is no denying that obesity is a psychological handicap, but mainly in the sense that it becomes the focus of a derogatory attitude towards one's self which is the much more fundamental disturbance and which plays an essential role in the very development of obesity.

THE PSYCHOLOGICAL ASPECTS OF BECOMING OBESE

In order to understand the development of obesity, it is necessary to make a clear distinction between the mechanism of becoming fat and stimulus that sets the mechanism into operation; or, to express it differently, between the "how" and the "why."

As to the "how" there is no doubt left that obesity is the result of a positive energy balance, that means, a person becomes fat when his caloric intake is greater than his energy expenditure. In most obese

people this is brought about through a combination of over-eating and inactivity. From a caloric point of view the large food intake is usually of greater importance than the saving in energy expenditure through inactivity.

There is really nothing noteworthy about the fact that a person who persistently and grossly over-eats grows fat, particularly if at the same time physical exercise is decreased. Under normal conditions a decrease in activity is associated with a reduction of appetite. The unexplained question is *why* this normal regulation is disturbed in obesity. This question becomes answerable if we turn from physiological to psychological considerations. Eating and exercise, physiologically represented as calories in the energy balance, are at the same time very important aspects of a person's behavior. A systematic inquiry into the living habits of many obese people has revealed that these functions are endowed in the obese with an emotional meaning different from the normal. Food has an exaggerated positive value for the obese person. It stands for love, security and satisfaction. Muscular activity and social contacts, on the other hand, are associated with the concept of danger, threat and insecurity. The simultaneous occurrence of love of food and avoidance of activity becomes thus comprehensible.

Eating and activity acquire this peculiar emotional significance in a family setting which, though not specific, is characteristic for obesity. The typical obese family is of small size. Quite often it is the youngest or an only child who becomes obese. Fathers usually play a subordinate role in the emotional life of the obese family. The mothers are dominant in their influence and have a particularly close hold on the potentially obese child. Many mothers live out their own problems and frustrations in these children. They cannot give their children respect as individuals nor permit them independence and the dignity of personal achievement. These mothers try to realize in their children their own dreams of a life of luxury and idleness of which they themselves may have felt deprived. Their expression of affection is over-feeding the child and sparing him the necessary tasks of doing things for himself. The mother's attitude towards the obese child is like that toward an inanimate and prized possession, one to which they give the very best of care in order to retain it. A characteristic aspect of this possessive attitude is the frequently expressed wish for a daughter instead of a son, because these mothers feel that a daughter represents a more permanent

possession than a son. In bringing up their sons they give them the role of a daughter in their emotional life. The "feminine" characteristics of obese boys seem to be related to this attitude of the mother. There certainly is no evidence that it is an expression of gonadal dysfunction.

Mixed with the expression of affection, which over-protectiveness and over-feeding represent, is an underlying hostility which many mothers feel in relation to the fat child. Far-reaching protective measures are devised to spare the mother the anguish of her own anxiety for the safety of the child, even though these measures interfere with the child's normal psychological growth and social adjustment. At the same time the mother is irritated by the demands which this excessive care makes upon her. She nags and criticizes the child and often resorts to beating him in order to find relief from her own exasperation. Yet in her heart she wants to retain his affection and loyalty, and food is a constant bribe with which she keeps him close and dependent. As long as the child is young there is prestige for her in having a well-fed child. As the child grows older and the obesity becomes a handicap the mother is likely to be the first to nag and belittle him for his awkward appearance and to berate him for his greediness.

The family frame of obese children thus reveals influences which lead to inactivity and over-eating and distort their personality maturation. The most serious aspect in this mal-development is the interference with the development of an adequate sense of security, competence and worth-whileness. The obese child grows up with a fundamentally low self-esteem and with the conviction of his helplessness in a world which has been represented to him as a dangerous place in which he is lost without a protecting mother. Such an attitude toward life makes an individual a constant victim of uncertainty and anxiety. His only defense against this anxiety is to turn back to mother; and since the mother has been a person who was unable to give of herself but had appeased all his needs with the offering of food, food becomes his weapon against anxiety and source of comfort in periods of emotional stress. For many obese people eating is the only known source of comfort and satisfaction. Other sources of satisfaction, comfortable relations to people and the realization of inherent creative and constructive abilities, have remained seriously crippled under the unfavorable influences of his upbringing.

The first systematic inquiries into the emotional background of obesity were made on obese children.^{5, 6} Numerous observations on obese adults show that there are amazingly little differences in the psychological problems between children and adults.^{7, 8, 9, 10} As a matter of fact, failure to develop true emotional adulthood is an outstanding feature of obese people. This means that in the course of development the necessary emotional changes which "growing up" implies have not taken place, because every change means abandoning of old satisfaction, a step which obese people are reluctant to take. Many obese adults, like fat children, are emotionally immature, passively dependent and helpless in meeting the exigencies of life. They seek comfort in over-eating in the face of failure and of frustrating experiences.

A woman of thirty described this misuse of food in periods of emotional stress as follows: "Sometimes I think I'm not hungry at all. It is that I am just unhappy in certain things—things I cannot get. Food is the easiest thing to get that makes me feel nice and comfortable. I try to reason with myself and tell myself that these problems cannot be solved by eating." She was one of the many fat people who succeeded in showing a fairly complacent attitude towards the world during the daytime but who became tense and anxious when alone at night. As she describes it, "I think then that I am ravenously hungry and I do my utmost not to eat. My body becomes stiff in my efforts to control my hunger. If I want to have any rest at all—I've got to get up and eat. Then I go to sleep like a new-born baby."

The comparison to a "new-born baby," that is, an infantile type of reaction, is a fitting description and may well be applied to the inability of fat people to tolerate frustration or postponement of satisfaction. Though most marked in relation to food, it can be recognized in many other aspects of their behavior. Fat people are described as placid and submissive and this is often correct as far as outward behavior goes. Their fundamental attitude towards life is demanding and they do not tolerate denial of their wants. Since the genuine solution of life situations is not always available or would entail an effort on their part, food is resorted to over and over again as a substitute satisfaction.

Many of the personality features are not limited to obesity but are met with in other forms of emotional mal-development and neurosis. The specific aspect of obesity is the utilization of food for obtaining

immediate gratification or as defense against anxiety. This perverse indulgence in food is often followed by a sense of guilt and moral inferiority which in turn leads to more eating. Unless this cycle is interrupted a person will persist in being fat however much he wants to reduce his weight. I just wish to add that obese people may suffer from many other symptoms which are commonly recognized as neurotic manifestations.

PSYCHOLOGICAL ASPECTS OF TREATMENT

Awareness of the underlying psychological factors leads to an understanding of the question why obesity has always presented such a baffling therapeutic problem. Viewed as a disturbance in energy balance, the treatment of obesity should be a very simple task. Reduction of the food intake and increase in exercise should and actually does accomplish a corresponding loss in weight. There is only one difficulty which makes the physiological prediction so uncertain in its clinical application. The fat patient just will not adhere to the perfect, well-balanced reducing diets which we prescribe, nor does he follow our advice for more active participation in social life that should make for his greater happiness and better adjustment.

It was this notoriously poor coöperation, particularly flagrant in the case of obese children and their parents, that prompted us at Babies Hospital to inquire into the life stories and living habits of fat people. This investigation had been at first part of a study on the endocrine factors in obesity. The observations on the growth and development of obese children which we made in the course of the investigation, stood in striking contrast to the then current assumption that hypothyroidism or hypopituitarism, or even hypogonadism were causative factors in obesity.

Looking upon the obesity problem from a historical point of view it is truly amazing that the quintessence of the cause and cure of obesity had been known since the time of antiquity. It seems that it was the application of the knowledge in the treatment of fat people which so often was found to be disappointing. The continued effort to understand this discrepancy seems to have led to many ludicrous theories about the cause, and to elaborate but useless programs of treatment of obesity. In a booklet called "Cursory Remarks on Corpulence; or Obesity Considered as a Disease: with a Critical Examination of An-

cient and Modern Opinions, Relative to Its Causes and Cure," published in London in 1816, the author, William Wadd, Surgeon,² summarizes the therapeutic practices of the ancient past and of his own time by saying: "The person who depends solely on the benefit to be derived from the use of any of them, will find himself grievously disappointed." He mentions as remedies the chewing of tobacco, fennel water, acids of various kinds, soap, eating of much salt to increase the absorption of fat by producing thirst, etc. Wadd proceeds to outline a plan of treatment which would be useful today even though his theories on nutrition and metabolism may sound quaint. He understood very well the reasons for the many fanciful regimes which he discards as useless: "The idea of a specific is peculiarly flattering to a patient, for whilst it encourages an implicit reliance on a single remedial process, it tends strongly to shake his confidence in the slow and disagreeable operation of diet and regimen. A gentleman who was fond of good living, and found himself becoming more corpulent than he thought convenient, having heard of the salutary effects of Mr. Wood's regimen, ordered his cook to prepare the miller's pudding, which he ate with great regularity every day after his usual dinner."

He further explains: "Many would willingly submit to any violent remedy, so that an immediate benefit could be produced; but unless the disease speedily gives way, they despair of success; consider it as unalterably connected with their constitution, and of course, return to their former habits." Wadd's remarks are as pertinent today as they were in his time. It seems that each generation has to rediscover the simple basic facts about causes and cure for obesity. Fifty years later Banting¹ in his Letter to the Public reported how he had been searching for help for many years, consulting one "high orthodox authority (never an inferior adviser)" after another and how he received many conflicting and abstruse prescriptions, all in vain, until he found the "excellent adviser" in whose honor he publishes the account of his cure which he calls "simply miraculous." Banting exclaims "Oh! that the faculty would look deeper into and make themselves better acquainted with the crying evil of obesity—that dreadful tormenting parasite on health and comfort. Their fellow men might not descend into early premature graves, as I believe many do, from what is termed apoplexy, and certainly would not during their sojourn on earth, endure so much bodily and consequently mental infirmity."

The diet which Banting outlined has been included under his name in medical textbooks. Its main features, the elimination of bread, butter, sugar, beer and potatoes are in good agreement with the diet which we would calculate today. Yet the search for more specific explanations and more specific treatment of obesity has continued, and we are just now emerging from the promise and allure of miracles to be worked by endocrine treatment.

This repetitious cycle of overlooking plain facts about obesity and of clinging to high-sounding theories may be understood if we take psychological factors into account. The correction of faulty eating habits is a central problem in treatment. Yet the importance of over-eating has been most often overlooked in the medical treatises on obesity. The occurrence of alimentary obesity, the simple or exogenous as it has been called, has never been entirely denied and it has been included in the medical classification of obesity, only to be cast aside as not quite worthy of serious scientific endeavor.

One of the reasons for this neglect of over-eating may be found in the fact that obese patients usually are very vague when asked about their eating habits. They just do not tell us how much they eat, sometimes in good faith because to them it is not "too much," more often because they are ashamed to admit it. If obesity on the whole has been looked upon in our society as a problem with little dignity, this is even more the case for the moral evaluation of over-eating or gluttony. Over-eating is looked upon as a moral weakness and self-indulgence. Even physicians may express a sarcastic attitude. I quote from the monograph of a modern writer:¹¹ "There is only one kind of alimentary obesity, and there are only two adjectives which can suitably be used to describe it, namely, contemptible and disgusting. Every degree of alimentary obesity is contemptible, because it denotes self-indulgence, greed and gormandizing; and most are disgusting because they represent an unsightly distortion of the human form divine, and a serious impairment of the intellectual faculties." Little wonder that this doctor, who I am sure wants to treat his patients with respect and human understanding, has to find other causes for obesity and sets out to prove that most patients are fat from "causes which are endocrine and not alimentary."

The obese patient is more than ready to accept such a so-called scientific diagnosis. It makes him the victim of some mysterious fate

and he himself does not need to exert any effort or to assume responsibility for a change in his living habits. As we have seen, the basic attitude toward life of a fat person is passive and demanding and he expects to have everything done for him. His ideal of treatment is something, anything, that will melt his fat away without effort on his part such as the "ideal drug" of the ancient Cretans, the secret of which was lost already to the old Greeks, if such a drug ever existed. It sounds too much like wish-fulfillment in the Golden Age for fat people.

Even if such a drug existed, the best it would accomplish would be a purely symptomatic treatment producing "thin fat people." By this expression I mean to say that if the fundamental attitude and life habits of fat people remain unchanged they will regain the lost weight, if not immediately, then as soon as they are faced with problems that challenge their low capacity for independent decisions and achievement.

The basis of rational treatment of obese patients is an understanding of and respectful attitude towards their genuine problems. If an obese patient, particularly the fact that he over-eats, is approached with a respectful tolerance, he is not only more frank in giving information but his efforts at reducing will be more genuine and lasting. While on a reducing diet he needs the sympathetic support of a physician who will also help him to gain insight into the nature of his real problemis. This can best be accomplished by regular and continuous contact. Prescription of a diet alone is rarely sufficient. The dependent attitude of an obese patient is as much a fact of his existence as his over-eating. If we are aware of this problem we can utilize his visits to help him to achieve greater independence.

If, in order to insure regular visits to the office, some prescription is given, this will not interfere with a rational psychological approach as long as the drug is not presented as a magic pill that will do the job. There seem to be some drugs on the market which are said to have a curbing influence on the appetite and they might therefore be of direct additional help. There is, however, strong psychological objection against the use of endocrine products for treatment of so-called sexual mal-development in obese boys.¹² Cases in which there is true indication for such treatment are so exceedingly rare that they can be neglected for our discussion. In a very large number of obese pre-adolescent boys who are made the object of such therapeutic zeal, there is no medical justification whatsoever of exposing the family to unnec-

essary expense and the young patient to the emotional trauma of being branded as suffering from an essential physiological deficiency. Such young people are already handicapped by grave adjustment problems due to the difficulties of their background and the embarrassment of being fat. The additional psychological trauma of such unwarranted diagnosis and treatment further aggravates the situation since it seems to confirm their worst fears about being inadequate for life.

SUMMARY

I have presented tonight a concept which treats obesity as the somatic expression of a mal-development in personality maturation. The large physical size represents symbolically the need and desire for strength and security which the fat person lacks in his human relationships. The bodily expansion may be looked upon as a vicarious expression of a thwarted personality development. The leading traits which collaborate in the production of obesity, namely, over-eating and under-activity, have in themselves a high emotional significance. They serve as a defense against anxiety and give a semblance of satisfaction which the obese person has not learned to achieve in more constructive ways.

A modern writer¹³ expresses the inner awareness of a fat person that his creative potentialities are locked within him, far out of reach, by saying: "Imprisoned in every fat man, a thin one is wildly signaling to be let out." This seems to me to express the essence of the obesity problem.

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STUDIES IN INTERMEDIARY METABOLISM CONDUCTED WITH THE AID OF ISOTOPIC TRACERS*

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FROM time to time, in the development of science, man has come upon a tool or technique of such obvious importance and usefulness that numerous workers in various fields have seized upon it and applied it to the solution of their problems. The discovery of logarithms in mathematical science, the perfection of the microscope in morphological science, or the development of microrespirometry and the tissue slice technique in biochemical science, may serve as examples in which, in each case, the new tool tremendously accelerated the advancement of the science, simplified the solution of many problems and made possible successful assault upon problems which had previously been unassailable. Such a tool is the currently much publicized isotope technique.

It should be stressed at the outset that the application of this technique to biochemical problems does not constitute a new science in any sense of the word. It is a new tool, and one which is very widely useful in the solution of certain types of problems. It is indeed essential for the solution of some. There are, however, many problems in the successful investigation of which isotopes are of no use whatsoever, and it must not be imagined that the isotope technique in any way supplants the classical procedures of biological investigation, synthesis, isolation, analysis, and so forth.

The use of labels in biological studies antedates by many years the use of isotopes. Perhaps the most celebrated example of this type of study stems from Knoop,¹ who labeled fatty acids by the expedient of replacing a hydrogen atom on the terminal methyl group by a phenyl. Such a molecule could readily be distinguished from other molecules of fatty acid, by virtue of its altered chemical properties, and its fate in

* Given October 10, 1947 before the Twentieth Graduate Fortnight of The New York Academy of Medicine.

the animal body could thus be followed. The very strength of this method, however, was also its weakness. Just as the chemist was able to distinguish between the labeled fatty acid and the naturally occurring unlabeled analog, so, it was feared, might the experimental animal. It might handle the labeled material by a different route or at a different rate than the naturally occurring substance and, therefore, whereas one might glean a great deal of information about the behavior of the synthetic labeled compound in the animal body, one had still to be cautious in the translation of these results to the natural analog. What was needed, clearly, was a label such that the operator could at all times detect its presence and yet so subtle that the experimental animal was unable to distinguish between labeled and unlabeled molecules. Precisely such a label has been supplied by the currently available isotopes of the biologically important elements.

If one prepares a sample of some substance which occurs naturally in the diet or in the body of an animal, operating in such a way that one or more of the constituent atoms are replaced by atoms of the same atomic number but of different atomic weight, the product which one obtains is, in general, indistinguishable by ordinary chemical means from the naturally occurring material. Not only do chemical means fail to distinguish the synthetic from the naturally occurring substance, but similarly the experimental animal is incapable of telling the one from the other. The application of suitable physical measurements, however, permits the operator not only to tell the difference between two samples, but also to determine, with high precision, the composition of any mixture of the two.

In the study of intermediary metabolism, the customary procedure is to subject the animal to some known trauma and to observe the effect of this trauma upon the metabolic processes. The withholding of some normal dietary constituent, the addition of some abnormal dietary factor, the administration of a drug or other agent, the performance of some surgical procedure upon the experimental subject, these and other insults have found usefulness in metabolic studies. A difficulty which inevitably arises in the interpretation of the results of such experiments is the matter of the extent to which the insult has rendered abnormal the metabolic process under investigation. By way of example one may cite the numerous studies of glycogenesis in which the rate of reappearance of glycogen in the liver of the previously fasted animal has been

observed. The preliminary fast, which provoked a decrease in the quantity of liver glycogen, was a necessary condition for such an experiment. Whereas the results of such a study would yield much information about the rate of glycogen synthesis in the liver of the previously fasted animal, one had to be cautious in the translation of such information to the normally nourished animal. The experimental insult was of such magnitude that it might well have influenced the very rate which was sought.

Of all the various experimental traumata at the disposal of the biochemist today, probably the one which is least traumatic is the replacement of some normal dietary constituent by the same chemical compound, some of the atoms of which are isotopic. Indeed, so slight is the trauma incident to this procedure, at least in the case of the non-radioactive isotopes, that there is no evidence whatsoever that any alteration in metabolic processes follows. Yet the study of such animals may yield a great deal of information, as will be seen from the experiments to be described, information which was essentially unobtainable prior to the development of this technique.

In discussing the problems of intermediary metabolism in which the application of the isotope technique has proven most successful, it is convenient to consider several categories in terms of the question which is raised by the investigator.

Is compound A synthesized by the tissue or the animal under investigation, or is it not?

If it is synthesized, from what precursors is it formed?

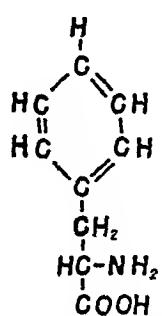
In the animal at constant weight, composition and nutrition, at what rate is tissue constituent A being destroyed and replaced by newly synthesized material?

How are these rates affected by such variables as change of diet, disease, drug or hormone action, growth, and so forth?

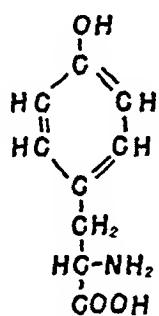
To illustrate the first category of question, I have selected as an example some work coming from Chaikoff's laboratory.² The question asked was quite simple: Is thyroxine synthesized in tissues other than the thyroid, or is it not? It is self-evident that if any thyroxine is synthesized in the body of the totally thyroidectomized animal, it must be very scanty, probably too little to permit of satisfactory isolation and identification by conventional chemical means. Were this not so, one would not expect to find the symptoms of hypothyroidism to follow

thyroidectomy. The workers therefore resorted to the tremendously sensitive isotope technique, taking advantage of the fact that the synthesis of thyroxine involves the uptake of iodine, and that the administration of radioactive iodine to an intact animal is promptly followed by the appearance of radioactivity in the thyroxine formed. Rats were first subjected to thyroidectomy which was subsequently proven to have been complete. Into these animals were injected minute amounts of potassium iodide containing radioactive iodine, and from the proteins of several tissue fractions, extracts were prepared which would contain thyroxine, were it present. The fact that each of these fractions was radioactive gave indication that thyroxine containing radioactive iodine had indeed been synthesized. To make the argument completely convincing, the workers now added to some of these fractions samples of ordinary, nonradioactive thyroxine, and then re-isolated thyroxine from the mixture. This procedure, the so-called carrier technique, is based upon the fact previously mentioned that isotopic and nonisotopic variants of the same molecular species are chemically identical, and consequently cannot be separated from each other by fractional crystallization. The normal thyroxine which was added would therefore become inseparably mixed with any radioactive thyroxine present in the tissue extract, and when thyroxine was re-isolated, in pure state, it would now be radioactive. This was precisely what was found to occur. The re-isolated pure thyroxine not only exhibited radioactivity, but repeated further recrystallizations, designed to separate thyroxine molecules from all other contaminating molecular species, did not produce any alteration in the quantity of radioactivity. The authors therefore necessarily concluded that atoms of iodine, administered in the form of inorganic iodide ions, were incorporated into thyroxine molecules in the tissues of their rats, this despite the fact that all vestiges of thyroid tissue had previously been extirpated. It therefore follows that the synthesis of thyroxine can and does occur in tissues other than the thyroid gland.

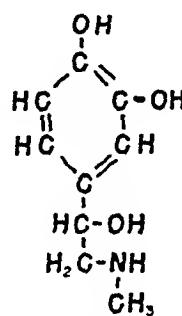
These experiments may serve to show how isotopes may be applied to the study of questions of what we have called the first category. Numerous examples might have been cited but the one selected happens to be of endocrinological interest and hence seems particularly suited to the subject matter of the present meetings. The endocrinological implications have similarly dictated my selection of an example of a



Phenylalanine



Tyrosine



Epinephrine

study falling in the second category: What is the precursor from which a compound is formed in the body?

The similarity in structure between phenylalanine, tyrosine and adrenaline has been apparent for many years, and in view of the fact that of the benzenoid amino acids only phenylalanine is required in the diet, it has been tempting to postulate that the other two compounds are made from this indispensable precursor. Until the advent of the isotope technique, however, convincing evidence bearing on this point was not at hand. The first attack upon the problem was made in Schoenheimer's laboratory³ when phenylalanine, labeled with deuterium, was synthesized and fed to experimental animals. The tyrosine subsequently isolated from the proteins of the tissues of these animals was found to be rich in deuterium, a finding which required the conclusion that by fairly direct means, phenylalanine had been oxidized to tyrosine in the animal body.

The second attack on the problem was somewhat more subtle. The isolation of sufficient adrenaline for isotope analysis from the adrenals of a small experimental animal was entirely impractical. Gurin⁴ has recently resolved this difficulty by resorting to the carrier technique mentioned previously. In a recently reported series of experiments, the preparation of two different samples of isotopic phenylalanine was described, the one labeled with radioactive hydrogen of mass 3, tritium, the other labeled with radioactive carbon C¹⁴. Each of these materials was injected into rats, and after a short time the rats were killed and their adrenal glands extracted. A small amount of non-isotopic adrenaline was now added to the extract and from the mixture, adrenaline

was re-isolated. This adrenaline, after careful purification, proved in each case to be radioactive, and the authors therefore concluded that adrenaline is formed at the expense of phenylalanine. In this direct and conclusive fashion has the precursor from which the body manufactures adrenaline been identified.

The examples of successfully terminated studies in which precursors of biological compounds have been identified by the application of the isotope technique are very numerous. The foregoing example will suffice to show the type of evidence that is obtained. The suspected precursor must in general first be synthesized so as to contain one or more isotopic atoms. This material must then be administered to the experimental animal and the suspected product isolated from its tissues or excreta. The demonstration of high concentrations of isotope in the product will in general mean that it has been formed from the precursor which had been administered, and there will be very little question about the interpretation of such a result.

Problems of the third and fourth categories, those relating to rates of reactions occurring in the animal body, are often a little more complex. If one considers the normal animal at constant weight and on a uniform diet, hence presumably of constant composition in regard to body constituents, the question of the rates at which these constituents are being destroyed and simultaneously replaced by newly synthesized materials is clearly not an easy one to answer. For example, in such an animal the quantity of fatty acids in the depot fat will be constant from day to day. Yet this fat is not dead tissue, it is alive and may therefore be presumed continuously to be undergoing mobilization and destruction. The processes leading to the formation and deposition of new fat must also be proceeding, and under our conditions, must be proceeding at the same rate as the destructive processes, if the quantity is to remain constant. Starving such an animal, to deplete it of depot fat, and subsequently observing the rate of regeneration of fat on a controlled diet, will not suffice. In the first place, as mentioned earlier, the previous fast may of itself disturb the rate in question. In the second place, and perhaps more important, the rate at which fat reaccumulates in such a fasted animal is at best only the difference between the rate of deposition and the rate of mobilization.

The isotope technique offers two experimental procedures which may be employed in the evaluation of these rates. In the first procedure,

an isotopic precursor of the body ingredient under investigation is administered to the animal, and observations made, over a period of time, on the rate at which isotope accumulates in the tissue constituent. As newly synthesized molecules, each of which now will be isotopic, replace the pre-existing non-isotopic molecules of the reservoir of the substance in the body, the substance will progressively become richer and richer in isotope, approaching asymptotically some maximal value which will be determined by the quantity and isotope concentration of the precursor administered, and the reactions involved in the synthesis. Clearly the rate at which newly synthesized molecules are replacing pre-existing molecules will be related to the rate at which the isotope concentration is approaching its maximum, and in many cases, the analysis of such data permits the estimation of "turn-over" rates.

Still another procedure involves the administration, not of a precursor, but of the material itself, suitably labeled with one or another isotope. This material will, in many cases, mix with the body's store of the same compound, and in this way a labeling of the body's store will have been effected. After this preliminary operation, isotopic materials are withheld from the animal and observations made on the rate at which isotope disappears from the reservoir of compound in the animal body. In this type of experiment the newly synthesized molecules will be non-isotopic, and as they replace the pre-existing, in this case isotopic, molecules, the isotope concentration will fall, approaching zero at infinite time. Again the rate of change in isotope concentration will be mathematically related to the rate of turnover of the molecules of the tissue constituent under consideration.

Both of these procedures, if properly applied to the same body constituent, will in general give the same numerical answer for the turnover rate. The selection of procedure is often dictated by the convenience of operation or the cost of isotope required. The exact analysis of data obtained from such experiments often requires various assumptions, such as perfect mixing in the body, but the results which have been obtained have, in general, justified the assumptions which are needed.

As an example of the use of isotopes in the study of rates of turnover of body constituents in the normal animal, I should like to cite some experiments carried out by Dr. Boxer and myself⁶ in which we investigated the rates of synthesis of fatty acids and of glycogen in normal rats maintained at constant weight on a uniform diet. The isotopic

precursor administered, perhaps the simplest one that there is, was deuterium oxide, heavy water, it having previously been shown that the hydrogen atoms of water contribute to the fatty acids and to the glycogen which is synthesized in the body. By the administration of heavy water we achieved a labeling of the hydrogen atoms of the body fluids. At suitable time intervals thereafter, animals were killed and samples of fatty acids and of glycogen were isolated from their tissues and these in turn were analyzed for their content of deuterium. As was anticipated, with the passage of time the concentration of deuterium in these several substances rose, and from the rate of rise in isotope concentration it was possible to calculate the fraction of each material which was synthesized each day. Since the animals were in a uniform state, it must be supposed that a similar fraction was destroyed daily. Combining this information with the quantities of materials found in the various tissues, it was possible to calculate the number of grams of glycogen and of fatty acids synthesized each day by a normal rat and it turned out that less than half a gram of glycogen and about two grams of fatty acids were thus being turned over. Comparison of these quantities with the quantity and composition of the diet consumed each day revealed that only about 3 per cent of the dietary glucose was finding its way into glycogen whereas about 30 per cent was being used each day to maintain the body's depot of fat.

Employing essentially the same technique, my colleagues and I⁶ have extended this study to include the alterations of these rates that occur in certain abnormal conditions. For example, we have compared these same rates in normal rats and rabbits and in animals rendered diabetic by the administration of alloxan. This poison has been shown to exert a selective destructive action upon the beta cells of the islets of Langerhans, and hence to diminish the supply of insulin to the body. In such diabetic animals it was found that glycogen continues to be formed, but the rate of its formation from glucose of the diet was markedly reduced. More striking, quantitatively, was the decrease in the rate of fatty acid synthesis in the diabetic animals, when compared with the normal. Thus, in our rats, it turned out that the production of diabetes resulted in a fall in this rate to a value of about 5 per cent of normal. A factor which must be considered, therefore, in accounting for the loss in depot fat in uncontrolled diabetes is the failure of the animal to synthesize fatty acids at normal rate, this in addition to the well-

recognized increase in the rate of mobilization and combustion of depot fat.

It is noteworthy that the converse of this effect may be observed when insulin is injected into an otherwise normal rabbit. Again employing the same technique we have been able to demonstrate that the rate of fatty acid synthesis in the liver of an animal receiving insulin is far greater than in the liver of the normal control animal. An increase in this rate to a value of about four times normal has been observed, a finding which should be given consideration in the explanation of the gain in weight which is observed to follow insulin administration to the normal as well as to the diabetic subject.

Another type of experiment may be described to indicate how yet another variable, change in composition of the diet, may affect synthetic rates in the animal body. It has long been recognized that in the rat a severe degree of fatty liver will follow the withholding of choline from the diet. This finding has been explained on the assumption that fatty acids normally leave the liver preponderantly or exclusively in the form of the phosphatide lecithin, a large molecule for the formation of which choline is necessary. On the usual protein-poor diet, the animal's ability to make choline is markedly curtailed, and hence the liver is unable to manufacture and discharge adequate amounts of lecithin, the fatty acids synthesized in or delivered to the liver are unable to escape and fatty liver supervenes. If this is the true explanation, the quantity of choline in the diet would be expected to determine the rate of lecithin synthesis. We⁷ have therefore prepared synthetic, isotopic, choline, labeled by the introduction of nitrogen of mass 15 in lieu of the normal nitrogen 14. During the first phase of the experiment, this material was added to an otherwise complete diet, and the rate of appearance of N¹⁵ in the choline of the lecithin of the rat's body determined. During the second phase of the experiment all choline was withheld from the diet. The isotopic nitrogen which had previously been introduced into the choline of the lecithin gradually disappeared, and the rate of its disappearance was followed. From these two rates of change of isotope concentration it was possible to calculate: Firstly, the rate at which the parts of lecithin were being assembled in the liver of the rat when choline was present in the diet; Secondly, the same rate when choline was absent from the diet, while the animal was developing a fatty liver. It was found that following the withdrawal of

choline from the diet, the rate at which lecithin was being synthesized dropped to about one third of the value which had been obtained when choline was present in the diet, this in spite of the fact that the total quantity of choline present had not changed appreciably.

Of the very many examples that might have been mentioned this evening, a few selected cases have been presented in terms as simple as possible in the hope that by so doing, an idea may be gained of the powers as well as the limitations of this method. I should like to state again, in closing, that this new tool supplements, but does not supplant, the earlier methods and conclusions of biochemistry. We have today at our disposal a label for molecules which is not only more physiological than the one that Knoop employed, but also in many cases easier to handle. Finally, I should like to record my conviction as well as my hope which is, in contrast to the impression of many popular writers on the subject, that this is not the last word in biochemical science, that the unanswered questions which will be brought to the surface by the isotope technique, or indeed by any other technique, will exceed in number the problems that it will solve.

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PENICILLIN TREATMENT OF SYPHILIS

WITH SOME REMARKS IN RETROSPECT OF SYPHILOTHERAPY
OVER ONE HUNDRED YEARS*

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IT is with deep humility that the speaker participates in this Centennial Celebration of the founding of The New York Academy of Medicine. Needless to say, it is a great honor. One hundred years! What great changes have transpired in general medicine as well as in syphilotherapy and in the entire scope of this protean malady.

A long list of well-known New York names comes to mind:

Edward L. Keyes¹ showed by repeated blood examinations that mercury in small doses had a tonic effect and was the author of "The Tonic Treatment of Syphilis" (1877). Edward L. Keyes, Jr., was also a syphilographer of note.

Robert W. Taylor² wrote "Syphilitic Lesions of the Osseous System in Infants and Young Children" (1875) and published a large folio entitled "A Clinical Atlas of Venereal and Skin Diseases" (1889). It contained many colored illustrations of cutaneous syphilitic lesions in different stages.

L. Duncan Bulkley's³ greatest contribution to syphilis was his "Syphilis in the Innocent" (1894) which won the Alvarenga Prize of The College of Physicians of Philadelphia (1891).

George Henry Fox⁴ in 1881 published an atlas of photographic illustrations colored by hand and containing 48 plates, the first time that photography was used to depict cutaneous syphilis.

Prince A. Morrow⁵ was an American pioneer in the prophylaxis

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of syphilis, a bent developed after his translation of Fournier's "Syphilis and Marriage" (1881). He founded the Society of Sanitary and Moral Prophylaxis in 1905 and served as its President. He was editor of its journal "Social Diseases" and also of "Morrow's System," a classic at the end of the century. Moreover, in this publication in 1901, W. R. Townsend,⁶ an orthopedist, gave an excellent description of heredosyphilis of the center of the face.

John A. Fordyce⁷ was probably the earliest pioneer in America in the treatment of neurosyphilis and wrote the article on "Etiology of Syphilis" in Morrow's System. Bernard Sachs was also a great student of syphilis of the central nervous system.

Sigmund Pollitzer⁸ was among the first American syphilologists to receive arsphenamine from Ehrlich and his "Serum Therapy and Serum Diagnosis in Syphilis" (1907) was among the earliest on the subject in our country. He was also one of the first to recommend multiple daily doses of the drug.

William B. Trimble⁹ first called attention to the mottled chin in syphilis, a manifestation of early syphilis and much more common in women.

Edward B. Bronson while a dermatologist wrote extensively on syphilis and Chas. Stedman Bull,¹⁰ an ophthalmologist of note, wrote the section on Syphilis of the Eye and its appendages in Morrow's System.

Historical: It may not be amiss to go back one hundred years and pick up a few salient items that will better show the meagre knowledge of syphilis at that time. It was generally recognized that syphilis was due to some contagious principle or miasm. Its course was partially recognized. The aftermath was not so clear.

John Hunter¹¹ propounded the dictum that syphilis and gonorrhœa were the same disease and that only primary syphilis and gonorrhœa were inoculable—that constitutional lesions and the blood were not inoculable. The work of Ricord,¹² A. Fournier¹³ and Auzias-Turenne¹⁴ in France, of Wallace¹⁵ in Dublin, of Bell¹⁶ and Foot¹⁷ in England and of many others, proved conclusively that generalized lesions of syphilis were inoculable and that gonorrhœa and syphilis were two different diseases.

Around 1840 to 1850 or 1860 there were several schools of thought in regard to treating syphilis. From earliest times there was one group

opposed to the use of mercury because of the terrific reactions resulting from the dosages employed. Many physicians felt that the price of health was the production of severe salivation—only then could the poison be eliminated. Chicoyneau, Chancellor of the University of Montpellier, tried to show the uselessness of salivation and rather to employ the method called extinction or elimination, i.e., restrained dosage (cited by Lancereaux,¹⁸ p. 293). It is not therefore, surprising that there have been published such volumes as "The Mercurial Disease" by Mathias,¹⁹ or the one by Kussmaul²⁰ on "Mercurialismus" and many others. As a result Thomson, Rose, Guthrie (cited by Lancereaux¹⁸) and others in England treated syphilis without mercury. Many in France did likewise and in this country, Harris and Stevens (cited by Lancereaux,¹⁸ p. 296). The Berlin syphilographer, Baerensprung (cited by Lancereaux,¹⁸ p. 306), formally repudiated mercurial preparations and used sudorifics and Russian baths. He claimed that he had never observed tertiary syphilis in patients thus treated.

Nevertheless, by the middle of the last century, in most cases, more sober judgement prevailed. Led by such men as Ricord, Diday, Fournier, Lancereaux and Chicoyneau in France, and by Sir Jonathan Hutchinson,²¹ Bell and Foote and others in England, mercury was usually the drug of choice. The protoiodide tablet was generally employed by Ricord and Fournier and hydrargyrum cum creta (gray powder) by Hutchinson. Inunctions were also employed and bichloride of mercury dissolved in various solvents and given under various names—van Swieten's drops, Dupuytren's pills, Cullerier's pills, Larrey's syrup, etc. Fumigations of cinnabar and calomel were commonly used in the first half of the last century and were still being employed at the end of the century. Moreover vaporizations of these preparations were still recommended as late as 1901 for pustulo-crustaceous syphilodermis by White (cited by Morrow^{5b}).

Girtanner used burnt sponge for venereal ulcers in the throat and Martini of Lübeck in 1826 substituted iodide with good results. In the same year Biett at the St. Louis Hospital successfully combined it with mercury. In 1831 Lugol reported cases of old syphilis cured by preparations of iodine alone (cited by Lancereaux,¹⁸ p. 300). Wallace²² of Dublin at the Gervis Street Hospital was the first to employ iodide of potassium, fix its dosage, point out its indications and place it almost on a level with mercury. He began his experiments in 1832 and gave the

results in lectures four years later. Ricord observed that tertiary lesions were more responsive than secondary manifestations (cited by Lancereaux¹⁸ p. 301).

Neumann²³ tells us that Christopher Hill, Blanton and Berkeley were among the first to employ subcutaneous injections of mercury and iodine compounds in the treatment of syphilis. In 1864 Scarenzio employed calomel. It was soon found that intramuscular injections were less painful and less prone to break down. At the Charité in Berlin, Lewin in 1867 used subcutaneous injections of mercury bichloride systematically in the treatment of syphilis, but it had already been employed by Hunter in 1856 and by Hebra in 1860. Gradually other mercury compounds were introduced. Silva de Araujo of Rio de Janeiro first used salicylate. Lang introduced the use of Oleum Cinereum (Gray Oil). Edward Bronson advised injecting the base of the chancre with a mercurial salt. At least it was as rational as cauterising it as recommended by Ricord in France and by Prof. Sigmund in Vienna.

Probably one of the most unusual methods of treating syphilis was by the so-called "syphilisation" work of Auzias-Turenne.¹⁴ He found that the person inoculated on further inoculations with the "chancreous virus," as he called it, gradually became refractory and without he or she having lost in the least good health and without showing effects of the disease. This work was taken up enthusiastically by Prof. Boeck²⁴ of Christiana and by Prof. Sigmund²⁵ of Vienna. Needless to say, it gradually fell into disrepute. In 1844 Auzias-Turenne claimed to have successfully inoculated a monkey with syphilis.

In the period when mercury and potassium iodide alone were used for treating syphilis, results in syphilis of the new-born were appalling. If the child did live, it lived a long life of recurrence after recurrence.

Arsenical Therapy of Syphilis: The discovery of the Treponema pallidum, the serologic investigations of Bordet, Gengou, Wassermann and others, the epoch making syntheses of the various Salvarsan compounds by Ehrlich²⁶ opened up a completely new era in the treatment of syphilis. At first the injections were given subcutaneously—the local reaction was profound and the effect on the disease far greater than anything achieved by mercury. The cure for syphilis had been found! Unfortunately, a few months later, more or less, the unfortunate patient and the physician learned otherwise. The next step was multiple injections and the elaboration by Ehrlich of further arsenical compounds.

Utopia had not yet been reached.

Bismuth Therapy of Syphilis: As far back as 1889²⁷ Balzer²⁷ had experimented on dogs with bismuth compounds but found them to be too toxic. Actually the dogs had died from an epidemic, presumably distemper, and not from bismuth. At any rate, he stopped further exploration on the subject. Then Robert and Sauton²⁸ showed the value of sodium-potassium bismuth tartrate in spirillosis of fowls. Sazerac and Levaditi²⁹ at the Pasteur Institute in Paris then investigated its use in syphilis. This was the beginning of another great cycle in syphilitotherapy and, incidentally, the elimination of mercury.

What has happened since is too recent to deserve more than mention. Best results were achieved with early diagnosis, with continuous treatment with alternating courses of arsenicals and bismuth, with careful follow-up of the patient. With intravenous drip or even with intensive arsenical and bismuth therapy, cure could be achieved at a price. Fever therapy even entered into the picture and malaria therapy, or with the fever box, was found to be of great value in central nervous system syphilis.

It seemed that almost the ultimate had been achieved in handling this protean disease. A large proportion of the patients with acute syphilis were being cured—under ideal conditions of early diagnosis and of thorough treatment 85 to 90 per cent. Not much more could be expected when the fourth great advance came on the scene—mercury, arsenic, bismuth and Penicillin.

Penicillin Therapy of Syphilis: This new antibiotic compound was discovered by Fleming³⁰ and elaborated by him and H. W. Florey.³¹ Its exact mode of action is not known. As Frazier³² puts it: "Perhaps it interferes with the normal completion of some metabolic action which interferes with the growth of the cell and which leads eventually to its death." It had been found to be especially effective in streptococcal, pneumococcal, and gonococcal infections—somewhat less so in staphylococcal conditions. Again to quote Frazier: "It is the most potent, yet non-toxic antibacterial substance yet applied to the treatment of clinical disease." Once more there arose in the minds of different students, what would it do in the treatment of syphilis? At least one most competent worker in this country explored the field in rabbit syphilis and had negative findings. The penicillin being used at the time was of a crude variety and various explanations might be supplied from the standpoint

of low unitage, impurities, etc. It remained for John F. Mahoney, Arnold and co-workers³³ at the Staten Island Hospital of the United States Public Health Service to report its successful use in the treatment of four cases of early syphilis through intramuscular injections of Penicillin Sodium given every three hours, day and night, for a total of 2,400,000 units over a period of seven and one-half days.

Since then, The Penicillin Panel of The Office of Scientific Research and Development of The National Research Council, The Syphilis Study Section of the United States Public Health Service and The Rapid Treatment Centers of the United States Public Health Service through Army and Navy and U.S.P.H.S. Venereal Disease Centers, and through University clinics and hospitals, have carried on an investigation on a large scale on the value of this drug in the treatment of syphilis. Much of the credit for success thus far achieved should go to Prof. A. N. Richards and Dr. Chester Keefer of the O.S.R.D., to Dr. J. E. Moore of The Penicillin Panel, and to Dr. Udo J. Wile in charge of the Venereal Disease Rapid Treatment Centers of the United States Public Health Service. Also, much credit is due Surgeon General Thomas Parran of the U.S.P.H.S. and to Dr. J. R. Heller, Jr., Head of the Bureau of Venereal Disease of the U.S.P.H.S. for taking over the penicillin project after the close of the war.

What are results of this coöperative investigation to date? Is the work finished? Do we have tangible results? Yes, but there is still plenty to be done, wrinkles to be ironed out, dosages to be determined, methods of administration to be evaluated, etc. All agree that in some way or other a method of ambulatory treatment is a pressing demand.

When the drug was first announced and in the enthusiasm of the moment, we were almost ready to admit that now the real cure for syphilis was at hand. Remember the same thing happened with Salvarsan (606)—the clinics were besieged with syphilitics demanding the “one shot cure.” Nevertheless, the situation with penicillin may be somewhat different and may promise an even better outlook than from the heavy metal therapy. At least it requires discussion under several categories.

Serologic Follow-Up of Patients: Throughout this entire discussion it is understood that the patient has already had a frank diagnosis of syphilis made clinically and either by darkfield examination or by acceptable flocculation and precipitation tests, including titration of

the reagin content of the serum. This is the base line from which the clinician must work throughout his entire follow-up of the case. One patient may be a sero-negative primary, another a sero-positive primary with 4 Kahn units, another perhaps a secondary syphilis with 64 Kahn units. This serologic titer may vary somewhat from day to day. Following treatment, the original titer perhaps of 8 Kahn units may rise to 32 in a period of a few weeks and then over a matter of several months perhaps drop to complete negativity. Again, the titer one month may be 8 units and perhaps the next 16 units—this means little of itself. It is the over all trend of the titration curve that counts—especially in early treated syphilis, in syphilis and pregnancy and in suspected or treated early congenital syphilis. A patient with early treated syphilis is not considered cured until his serologic titer has been completely negative for one year after completion of treatment. Also, he or she must have a normal physical examination, lumbar puncture and complete cardio-vascular studies. A persistent titer of 8 Kahn units over a period of 12 months in early syphilis would indicate sero-persistence and demand re-treatment. A persistently rising titer indicates trouble in a suspected primary or in a suspected congenital syphilis. In such cases a tiered specimen may be necessary every week or so. We reiterate, all penicillin treated cases of early syphilis require a monthly tiered serologic check-up, as well as physical examination.

Reactions from Penicillin Treatment: One of the great advantages of penicillin over heavy metal therapy lies in the absence of reactions³⁴—severe in type. While the Herxheimer reaction is seen earlier and is more intense than after heavy metals this is, if anything, favorable in an early syphilis. In a syphilis and pregnancy, or in a central nervous system syphilis or in a syphilitic nephrosis, it might indicate lowered dosage for the first two days. A generalized erythema is not uncommon and occasional cases of erythema multiforme and even of erythema nodosum have been seen. These are rare and dermatitis exfoliativa is exceedingly rare. We know of but one such fatal case reported by Barksdale.³⁵ Urticaria is occasionally encountered, especially after Penicillin Calcium P.O.B., and may not show up for several weeks and be quite troublesome. In rare instances the localized type with angioneuritic edema may ensue—this might be a serious complication and must be kept in mind. Fortunately, thus far, no severe involvement of the hematopoietic system has been reported. Barksdale has also seen some

cases of neuritis following penicillin therapy and we have also encountered one. In some instances "id" reactions on the skin have been seen in individuals suffering from dermatophytosis.

Routes of Penicillin Administration: The drug should not be employed orally or rectally in the treatment of syphilis—at least in the present state of knowledge. The dosage is inexact, absorption is problematical and cost prohibitive. While penicillin may be administered by intravenous drip, the difficulties of administration, of thrombo-phlebitis and of immobilization of the patient are too great. Intrathecal administration is also unwise because of reactions in the meninges, even leading to adhesive spinal arachnoiditis and transverse myelitis.³⁶

The desire in penicillin therapy is to achieve and hold a continuous high blood level of the drug. This may easily be obtained by intramuscular injections every two to three hours, provided sufficient dosage is employed.

Treatment of Early Syphilis with Penicillin Sodium in Saline or Distilled Water: Results of this form of therapy have been found to be successful in a large number of cases. In fact, they have been so successful that we are now seeing the phenomenon of reinfection on a far higher scale than heretofore. Some men would even put it as high as 20 to 30 per cent. This may be somewhat exaggerated, but it is actually frequently occurring. To attain this cure, it is necessary that the diagnosis be made as early as possible, that a sufficient dosage be employed and that the patient be followed with a serologic titered check-up every month until the reaction has been completely negative for one year. True, there has been a period recently where there was a change in the fractions of penicillin and the use of too much K³⁷ fraction which is rapidly destroyed in the body. This has now been changed and penicillin is made of G, F and X fractions. Crystalline G is now being used exclusively. Because of this and of the relapses occurring while so much K fraction was used, it is recommended that in sero-negative primary syphilis a dosage of not less than 3,600,000 units be employed (ninety injections of 40,000 units each every two hours, or sixty injections of 60,000 units each every three hours). For a seropositive primary or early secondary syphilis, this dosage should be increased to not less than 5,400,000 units (ninety injections of 60,000 units each every two hours or of sixty injections of 90,000 units each every three hours). With a late secondary syphilis, it would be well to

increase this dose to a total of 7,200,000 units over a period of 7½ days. In all cases, careful monthly serologic titered check-ups are necessary.

Treatment of Early Syphilis with Penicillin Combined with Arsenoxide and Bismuth: Many investigators lost confidence in penicillin as a result of the large number of relapses³⁷ encountered from the use of low dosage penicillin and from the results during the period in the last half of 1945 and early 1946 when penicillin sodium with an increased K fraction was being used. Moreover, Thomas³⁷ and others had already shown that penicillin therapy combined with arsenoxide had half the treatment failures seen with penicillin alone. Schoch³⁸ had also shown a somewhat similar situation with additive bismuth therapy. Thomas added 40 mgs. of arsenoxide daily to the penicillin schedule of 7½ days. O'Leary³⁹ has suggested four daily doses of arsenoxide, each 40 mgs., then the penicillin sodium was started on the 5th day, 40,000 units every three hours for a total of 2,400,000 units. On the last day of the penicillin schedule, a course of bismuth subsalicylate injections was started, 1 cc. of a 10 per cent suspension every five days. Heller⁴⁰ has recently reported the results of combined schedules of penicillin, arsenoxide and bismuth as used in the Rapid Treatment Centers under the direction of Wile. The combination of 1,200,000 units of Penicillin Sodium plus five injections of arsenoxide and three of bismuth subsalicylate over a period of ten days was satisfactory. The joint statement⁴¹ of the Committee on Medical Research, the United States Public Health Service and the Food and Drug Administration, suggests an additive dose of arsenoxide, 300 to 360 mgs., administered in divided intravenous injections of 40 to 60 mgs. each, over a total period of one to four weeks. It is emphasized by them, correctly, that there is an added risk if this arsenic be given over a period of seven to nine days and much less if it is drawn out over four weeks.

Late Latent Syphilis and Late Cutaneous and Osseous Syphilis: It is our feeling that in all late syphilis the patient deserves a preliminary course of heavy metal (bismuth) plus potassium iodide to obviate the danger of a Herxheimer reaction or of a therapeutic paradox with too rapid healing of perhaps vital structures and resultant scar formation and contractures. Following this, the course of penicillin, 3,600,000 to 5,400,000 units, may be administered. In late latent syphilis, the physician should not commit the error of treating a persistently positive serologic reaction.

Syphilis and Pregnancy: At the recent meeting of the American Academy of Dermatology and Syphilology in Cleveland, Ingraham⁴² reported that in 125 cases of syphilis in pregnancy there had been ninety-seven per cent success with penicillin. His two failures were in cases treated with 1,200,000 units of penicillin. He reported that investigations have shown the penicillin to penetrate the placenta from the tenth week on. His results have been amply confirmed by everyone who has investigated this field of syphilis. Ingraham thinks penicillin has no abortifacient effect or tendency to bring on a miscarriage. However, I think that in all pregnant women with frank secondary syphilis it is well to cut down the dosage of penicillin for the first two days to one-half, and then raise it to full dosage. For example, with a dosage of 40,000 or 60,000 units every two or three hours, it would be well to cut it down to 20,000 or 30,000 units for the first two days. All writers recommend that diagnosis and treatment be given as early as possible though even in the last month of pregnancy with a viable child it is possible to institute treatment and have a child born alive, but still showing its mother reagin. This will usually disappear by the third month. All such children should have monthly titered serologic tests. If the titer does not drop to normal or if there be a tendency for the curve to rise, treatment should be instituted. A child with titer remaining negative and with negative physical and radiologic examination for one year may be considered free from the disease.

Treatment of the Syphilitic Child: In the syphilitic babe, one must consider not only the syphilis but also the infant's general condition. It may well be that supportive measures will be as much in order as specific medication. Perhaps a few intramuscular injections of aqueous sodium bismuth tartrate, Searle, 1 cc., will lessen the Herxheimer effect in a feeble child. The Syphilis Study Section would recommend for infants a total dosage of 100,000 to 400,000 units per kilogram (2.2 lbs.). In older children the dosage may be on a unit for weight basis—with minimum dose of 60,000 units per kilogram corresponding to the minimum total of 3,600,000 units for the adult. The results are good, but not as good as in syphilis in pregnancy. Penicillin seems to be of little value for interstitial keratitis of late congenital syphilis—malaria therapy is preferable and, is, in fact, almost a specific.

Syphilis of the Central Nervous System: Outside of syphilitic meningitis, the value of penicillin is still debatable. While it has an adjuvant

value and furnishes a sense of well being, it is a problem requiring still more data before anything too definite can be offered. Penicillin added to malaria probably enhances the value of the fever treatment. True, opinions differ.

Penicillin Calcium in Peanut Oil and Beeswax—Ambulatory Treatment: What is needed above everything else is ambulatory treatment for syphilis. Cost of hospitalization would be obviated, the patient would lose no work and, too, that sense of secrecy so necessary in this disease would be assured. While it is too early to make a clear cut statement, the reports of Romansky et al.⁴³⁻⁴⁶ seem very promising after use of single daily intramuscular injections of calcium penicillin, 300,000 units, in peanut oil and 4.8 per cent beeswax (by weight), hereafter spoken of as P.O.B. There seems to be no danger of foreign body tumors and blood levels of penicillin after the above dosage remain at a therapeutic level for twenty-four hours in a large proportion of the cases and with its cumulation after successive doses should be even higher. Probably the patient should receive at least sixteen daily doses or, better yet, twelve daily doses of 600,000 units and, until the problem is clearer, adjuvant arsenical and bismuth therapy—perhaps ten arsenicals administered three injections the first week and twice a week thereafter and bismuth injections, twelve in number, to follow the penicillin.

A warning should be issued as to the use of this form of therapy. The injections must be given daily, not every other day, not every week or when the patient feels like it. It is not like giving an injection of a bismuth salt. The whole theory of its use is based on the injection of a daily dosage—otherwise, blood levels fall and a penicillin-fast organism may be developed and certainly relapse will occur and perhaps infection of others as all physicians treating syphilis have observed.

One of the real objections to the use of this compound is the careless manner in which physicians use it for the one day treatment of Gonorrhea. He is not observant enough of the case to look for possible beginning genital lesions nor does he follow his patient up with a monthly serologic check-up for at least four months to rule out a hidden syphilis contracted at the time of the gonorrhreal infection, but as yet not diagnosticable. All of us have seen far too many of these cases—with resultant infection of wives and sweethearts and relapse syphilis in the patient.

As in all other forms of penicillin therapy, titered serologic reactions

on these patients are a "sine qua non" until the monthly reactions have been completely negative for a period of one year. The great danger with this technique is that the patient and the doctor are liable to take the thing too lightly and neither one to realize his responsibility. Too often no titered serologic studies are made and the patient is not followed up.

From a few observations we have been able to make, irregular use of penicillin P.O.B. may lead to the production of a penicillin resistant organism which can only be treated with heavy metals.

CONCLUSIONS

And so our view of penicillin treatment of syphilis, along with some observations of syphilitotherapy of the past century comes to an end.

Of the drugs, Mercury, Potassium Iodide, arsenicals, bismuth and penicillin, mercury, at least, is relegated to history.

I am not sure but that in late syphilis the physician is making a mistake in forgetting potassium iodide at the onset of therapy.

Whether bismuth and arsenicals will also be eventually dropped, only time can tell. For the present at least, they are still of great value in cases relapsing to penicillin and bismuth especially for preliminary treatment of old syphilis to be handled by penicillin.

It is to be wondered what the next century will teach us in handling this old scourge of mankind. Perhaps some perfection of penicillin or of some other antibiotic worked out by a Fleming or Florey or Mahoney may close the book for good. At least this will be the desire of every medical man.

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SURGICAL MANAGEMENT OF DIABETES: INCLUDING AMPUTATIONS*

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THE surgical aspects of the management of diabetes divides itself into the diabetic who requires a surgical operation such as, the removal of a diseased gall bladder or appendix and the treatment of surgical conditions to which the diabetic is particularly subject, such as carbuncles or gangrene.

Life expectancy has increased from forty to sixty years in the last century with better medical and surgical control of epidemic and degenerative diseases and if like advances continue, twice as many people over sixty-five will be alive by 1990 as today. A much larger group of patients is arriving thus at the age when surgical procedures are to be expected. This is particularly true of the diabetic. Joslin this year estimates that there are one million diabetics in the U. S. A. There are ten times more admissions for diabetes to large hospitals today than in 1910. A figure of 2.8 per 1,000 admissions in 1910 at Bellevue is contrasted with 2.1 per 100 of all admissions at the Post-Graduate Hospital averaged for the last five years (Tables I and II). While before most diabetics died early of their disease or its complications, with increasingly improved medical management of diabetes and thus greater longevity more patients will reach this surgical age. A thorough understanding of their surgical management is important because one out of every two diabetics requires a surgical operation sometime before he dies.

In reviewing the literature on the diabetic who required surgery one is impressed with the great change that has occurred with diabetic control inaugurated with insulin. Surgery for the diabetic became safe that day twenty-five years ago. It has not been sufficiently impressed on many physicians, however, and at times procrastination and even ineffective therapeutic measures are utilized in place of necessary opera-

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TABLE I—NEW YORK POST-GRADUATE HOSPITAL

Clinic Attendance—Yearly (average of 5 years)

Total Clinic Attendance	124,308
Total Diabetic Clinic	1815
Total Diabetics in Vascular Clinic	1885 } 3700
.2% of all Clinic Attendance Have Diabetes	

TABLE II—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

<i>Diabetes Mellitus</i>			
5 Year Total Hospital Admissions	53,267	Average per year	10,653
5 Year Total Diabetic Admissions	1,160	Average per year	232
2.1% All Admissions Diabetic			

tions merely because the patient has diabetes mellitus. As long ago as 1890 Lord Moynihan said, "no one should be allowed to die of one disease because he has another." This has occurred in too many instances in the history of diabetes. It is to be emphasized that we may do all types of surgery on the diabetic. This includes emergency operations, elective surgery and even reconstructive and plastic surgery. The important point, however, is to have the patient under adequate diabetic control. This requires the careful coöperation of the internist and the surgeon. The patient should be handled jointly and where possible a combined medical and surgical type of service is the ideal. In too many institutions the interest of the internist or medical resident ceases when the patient is transferred to the surgical service and the reverse also is true. One of the foremost advances in handling problems of this type is the combined clinics and services in which the patient is followed from the time he is admitted by both the medical men and the surgeon. Such a clinic by its proximity and intimate exchange of interests soon develops internists with surgical viewpoints and surgeons who know there is more to diabetic management than the Benedict or Fehling test. One can hope for the establishment of more combined services in our hospitals.

TABLE III—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

Diabetes and Surgery

Added danger due to:

1. Metabolic imbalance

- Vomiting
- Diarrhea and hyperstalsis
- Starvation
- Dehydration
- Acidosis

2. Infection

- More organism reproduction
- Less insulin effect
- Acidosis confuses symptoms

3. Liver function failure

- Present in diabetes
- Present in surgical conditions

4. Vascular diseases

Operations on diabetic patients are potentially more dangerous because of certain fundamental weaknesses which patients with diabetes develop (Table III). To control the diabetic there must be a *metabolic balance*. After most abdominal operations there is usually a metabolic upset caused by several factors, one of which is *vomiting*. This may confuse the glucose-insulin regime both by a loss of food intake and by the development of acidosis. The vomitus should be inspected and estimated for food loss and this should be adequately replaced intravenously. Tests for acidosis must be run and this imbalance overcome. The starvation so often present prior to operations or in patients with such a debilitating disease as cancer may deplete the glycogen reserve. In these instances a febrile reaction may reduce the carbohydrate base to a dangerous level. A protein reserve must also be established prior to operation. Diarrhea and hyperperistalsis or the necessity of colostomy or ileostomy results in fluid loss and makes the diabetic control a more difficult problem.

Salt and water balance must be maintained. These are all potentially

dangerous metabolic problems which must be kept more in mind in operating on a diabetic. It illustrates again the necessity for continued medical management by the internist. If the diabetic receives 150 to 200 grams of sugar by mouth or vein in the twenty-four hours after operation with sufficient insulin to utilize it, the danger of acidosis will be slight.

Another source of potential danger to the diabetic is the *post-operative* infection (Table III). There is no evidence that infection develops more often in the diabetic but if an infection does develop, its progress and the loss of diabetic control are more rapid. In the presence of infection insulin is frequently ineffective and in the patient who runs sugar, organisms multiply more readily. This is adequately shown by a high death rate in ruptured appendix in the diabetic. Infection may rapidly direct a patient into acidosis and infection acidosis and acidosis may be difficult to differentiate immediately, as their symptoms are similar. Acidosis with malaise, general abdominal tenderness, pain and vomiting appears like any acute abdominal lesion and may mask an infection for some time. Prophylactic chemotherapy in the major procedures is valuable, particularly in bowel resections. The ability of certain drugs to reduce the bacterial flora in the body should be utilized particularly in these patients. Sulfasuxidine will so greatly reduce the colon bacilli in the colon that it should be part of a routine preparation for operations in this area. Better drugs are becoming available in the near future, and these will reduce further the infection incidence. The necessity for early recognition of a postoperative infection is greatest in the diabetic and diabetic control can be reobtained only when the infection is drained. In addition, operations on the diabetic require a more careful technique—large crushing clamps, heavy ligations and mass ties will be reflected in greater morbidity. Meticulous asepsis and hemostasis is more necessary in this group. "A minor technical error of little moment in the average patient may make the difference between success or failure." An example is the soiling of the peritoneum or wound edge by an appendix stump prior to its cauterization or inversion.

Nearly all diabetics develop liver changes which interfere with glycogen storage and biliary secretion and function. This is true particularly in the severe diabetics and may be sufficient to prevent good control. Many general surgical conditions also lead to liver dysfunction,

the biliary system being a particular offender. A diabetic liver will *not* stand biliary infection and stasis as well as a normal liver. Liver abscesses create a serious problem. Thus an acute cholecystitis will require rigorous diabetic management and early removal.

There are certain diseases to which the diabetic is particularly susceptible. Gall bladder disease has already been mentioned. Autopsies show that one-half of those dying of diabetes have gall bladder disease. These patients should be operated early, prior to the complication stage which will inevitably arise. One cannot expect surgery, no matter how expertly performed, to aid the patient whose liver has been destroyed. There are many doctors whose diabetic patients have diseased gall bladders who believe they are treating their patients correctly by delaying inevitable operations. We feel this is a disservice to the patients as the operation when eventually performed may be at a time when complications make a cure impossible. The risk increases and the ability to surgically cure decreases with the length of time the disease is present. Jaundice in the diabetic greatly increases the operative mortality, possibly due to preventing fat from entering the liver and allowing glycogen deposits. Disease of the pancreas is another condition which patients with diabetes often develop. An acute pancreatitis has been found to be present in one-fifth of all the patients dying in a diabetic coma. This again ties in with biliary tract diseases. Successful handling of such patients requires early operations, i. e., as soon as the diagnosis is made and diabetes controlled.

Goiter is a disease which is incompatible with diabetes. The hyperthyroidism with its rapid metabolism prevents control of the glycemia. Hyperthyroidism interferes with the storage of glycogen or increases its release by an adrenalin-like effect and it is antagonistic to the insulin action. Removal of a diseased thyroid will permit immediate and better diabetic management thereafter. The simple infections as well as boils and carbuncles in the diabetic have been emphasized sufficiently in the literature. Only by repetition, however, do we seem to acquire knowledge. The figure of 20 to 60 per cent mortality from carbuncle in the diabetic has been greatly reduced with chemotherapy, particularly penicillin. There are exceptions, however. One of my patients has had a carbuncle on his face approximately one a year for several years. He develops a leukopenia under sulfa drugs, the first time dropping to 900 leukocytes before the condition was understood. He is also

sensitive to penicillin and each time he appears with this infection of the face the gravity of diabetes and carbuncle is reimpressed on me. The treatment of this infection resolves itself into active and aggressive diabetic therapy and even greater surgical restraint. Chemotherapy must be used and the local wet dressing, if not traumatizing, may help in localizing the lesion and relieving the pain. One can hardly improve on Joslin's edict for the diabetic carbuncle or boil, "Do not squeeze, do not pinch, do not cut and do not run sugar." When there is fluctuation, of course, drainage shortens the course. In respect to these infections I would emphasize again my experience in the value of repeated small blood transfusions. The rationale of such therapy must be understood. It is not to replace hemoglobin and red blood cells but to supply some defensive factor in the circulatory medium in which the patient is deficient. This blood is destroyed by its host in a short time and this defensive factor needs replenishing in two or three days. Not only in the diabetic patient but in innumerable instances of severe infections during the recent war I have seen this factor be the determining one, even in the presence of adequate chemotherapy. The strengthening of the patient's defenses should not be neglected. The benefit of x-ray therapy in localizing these infections early should be remembered and utilized in selected instances. Prophylactically, Brigham emphasized the value of hygiene with, "the washed neck like the watched pot never boils."

The diabetic is as susceptible to the acute abdominal conditions such as appendicitis, or diverticulitis as any other patient. The diagnosis in these instances may be difficult as acidosis may confuse the symptoms or delay the diagnosis. Frequently, the symptoms are insidious and many rupture early. While acidosis causes general abdominal pain and tenderness, a localized tenderness should make one suspect a surgical condition especially if it persists for a few hours despite diabetic treatment. It is well to remember that in a ruptured appendix the diabetes may never be controlled until the peritonitis is drained. In case of doubt operation always should be performed.

Carcinoma.—More operations for cancer are performed today on the diabetic than ever before. The diabetic also is more susceptible to certain carcinomas than other patients. Carcinoma of the pancreas has been found in one-third of the patients who died of diabetes (McKittrick) and one-half of those in Conlin's series.

When the diabetic comes to operation his general medical status should be determined. If the patient is elderly and shows the degenerative arteriosclerosis or cardiovascular change inherent in his disease, the risk will be greater. If not and with diabetic control and management throughout the illness, the mortality should be approximately equal to that of non-diabetics of the same age and in equal status of their cardio-renal vascular systems. We believe it is better if the patient is allowed to run a little sugar. The margin of safety is greater and one is able to tell more readily, the patient's status if shock or coma occurs.

Choice of the Anesthesia.—Local anesthesia is extremely valuable in operations on the abdomen or head but its shortcomings should be understood. Local anesthesia causes increased skin tension and trauma. For this reason it is contraindicated absolutely in operations on the extremities. Some prepared solutions contain adrenalin. Adrenalin is a vasoconstrictor and sugar liberator and should never be used in the diabetic. The various local solutions such as ethyl chloride are likewise contraindicated. Of the inhalation anesthetics cyclopropane is most effective. Ether or chloroform should be avoided. Nitrous oxide with its anoxemia may cause difficulties, especially in a heavily pre-medicated individual. Spinal anesthesia, except in the older age group, is probably the anesthesia of choice for the abdomen. The hypotension accompanying the anesthesia must be prevented if there is marked sclerosis of the peripheral or coronary arteries. Refrigeration anesthesia for operating on the extremities is ideal and will be discussed under amputations. The patient stands a rapid operation more readily than a long one. Glucose and insulin to utilize it should be used during the operation. Postoperatively, the patient should have urine and blood sugars and CO₂ combining power run as often as the severity of the diabetes requires. The patients are particularly susceptible to acid base imbalance and their hydration must be maintained. The value of surgical care combined with medical management is reflected in the mortality figures of less than 4 per cent in over 1,000 major operations at the Mayo Clinic. Early ambulation will reduce the complications and should be utilized. In this early ambulation, non-absorbable sutures are needed. In our hands buried steel wire in the fascia best fulfills the requirements that the suture be strong, easily inserted and with minimal tissue reactions. The reduction of postoperative chest, abdominal and thrombosis complications by early rising we have emphasized before.

Peripheral Obliterative Arterial Disease.—It has been shown quite definitely that arterial sclerotic changes occur many years earlier than we previously thought. In an exhaustive study of all patients without symptoms who were working at forty years of age and over, Wright, Lake and myself reported an incidence of arterial sclerosis in 40 per cent as shown by x-ray and abnormal oscillometric readings. This was much higher than anticipated, but is in line with our present day feelings that sclerotic changes begin ten to fifteen years prior to the development of symptoms. In the diabetic this occurs earlier, especially in the femoral arteries. It is evident that the sclerosis begins as atherosomatous changes but involves the walls, too. Joslin's statement that of all diabetics over 40, one-half have femoral sclerosis and that all age groups develop it within five years after the diabetes is discovered may be modified slightly. Certainly, prior to the third decade its appearance can be delayed. Still, approximately one-half of all diabetics die of an arteriosclerotic complication. This group, then, are surgically the most dangerous. With the peripheral sclerosis we have two factors, occlusion and infection. While infection is absent or minimal we treat areas of necrosis and gangrene conservatively, the same as we treat the non-diabetic patient. Toes or sloughs are permitted to self-demarcate, the edges to epithelialize and the dead part to amputate itself. At times, non-traumatizing removal of a dead toe with a rongeur hastens the healing. Any part of the foot that can be retained is saved. No toe or foot amputation requiring anesthesia is performed in this stage. Undermining or pus collections are prevented by sterile soaks and conservative painless debridement of sloughs or saucerizing. To these measures are added three factors, all of which will require careful training of the patient, and it is a duty of the doctor to establish this training, as emphasized by Duryee. These factors are (1) the elimination of all smoking. The part that nicotine plays in patients with arterial occlusion is well established. The occlusion of small collaterals by spasm due to nicotine has been definitely proven. The fact that nicotine itself may be a cause of occlusion other than by spasms is not unlikely. The work of Wright and Duryee, Short, Johnson, Silbert and more recently Weinroth and Herzstein has emphasized this view and there is enough evidence to conclude that if the tendency to sclerose is inherent or acquired, nicotine may precipitate it. In addition, Lundberg and Lundberg have shown a rise in blood sugar of 50 per cent and higher by smoking two

cigarettes, apparently on an adrenalin stimulating basis. We who study and work on the blood vessel system and observe the great part that smoking plays, view with considerable apprehension the nicotine problem. With figures showing that up to 50 per cent of the population will die of cardiovascular renal disease and the certain knowledge that smoking speeds the rate of the disease, it seems time to consider whether the tobacco habit may not be a national scourge.

Youngsters are encouraged to acquire the habit from an early age. National advertising and radio broadcasts constantly extolling the virtues of cigarettes play their part. During the recent war free smokes and smokers made a cigarette a part of each man. Seriously wounded men were given a cigarette even before a dressing or plasma. While in half of the population this may not be too harmful, in the rest a habit of smoking will be definitely deleterious and perhaps one day the deciding factor in the loss of a limb or life itself. In everyone over fifty there is some degeneration present in the arterial tree and this is especially so in the diabetic. The great difficulty of breaking any habit is human and this is particularly true of the smoking one. We believe a campaign on hygienic and preventive medicine lines should have at least equal radio time with such a destructive factor as tobacco. Perhaps we are too vehement but when one has heard strong-minded men admit they cannot give up smoking even to save their limbs the tobacco habit becomes a true physical menace.

The second factor is the prevention of skin breaks and infection. This is of extreme and fundamental importance. It requires attention to a hygienic regime in which the feet are cleansed as often and as carefully as the face. Pressure points such as blisters, corns and calluses, and ingrown toe nails must be eliminated by correctly fitting stockings and shoes. Fungus infection, a frequent forerunner for the skin break necessary for secondary infections to enter, must be controlled. In this connection all caustic materials are dangerous. This includes the corn cures and the salicylic and benzoic acid compounds. A very simple preparation of potassium permanganate in from 1:5000 to 15,000 is safe and effective when used for twenty minutes every three to five days. The use of skilled and correct podiatry is important both in the clinic and home and instruction on nail care at home should be given. The third point is an effort to stimulate collateral circulation and reduce spasm in the blood vessels still functioning in the limb. One simple, adequate

TABLE IV—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

<i>Diabetes Mellitus</i>	
Amputation	Incidence—1940-1945
	Total 22
Incidence amputation per clinic visit0011
Incidence amputation per hospital admission.....	.018

measure is rest, another is the use of Sitz baths regularly. Postural changes of the Burger exercise type may aid and the Saunderson's oscillating bed is another helpful method. Pancreatic tissue extracts have a place in this therapy by their adrenalin-neutralizing effect. It is a little too early to state the part the anti-coagulants, heparin and dicumarol, may play in this respect but we are greatly encouraged by our work on some so far and they may be a decided addition to our therapeutic armamentarium. In a selected group in which spasm is particularly a factor, sympathetic nerve blocks and sympathectomy will prevent or delay the onset of gangrene. This is effected by increasing the capillary blood flows. While there may be some question as to the effect of sympathectomy on the blood supply of muscles, there is no question but what the skin circulation in selected patients is improved and it is in the skin that the gangrene first develops. If sympathectomy is to be helpful it must be performed before gangrene is present. We believe the poor statistical results previously reported from sympathectomy in arterial obliteration were due to the fact that the operation was performed on late cases where gangrene was present; hopeless problems already. Sympathectomy cannot replace dead tissue. If one reserves sympathectomy for those patients with peripheral arterial symptoms when blocks show adequate skin temperature rises, the procedure will be helpful. Sympathectomy was performed in twenty-four patients this last year with only one amputation thereafter necessary and this patient should not have had the sympathectomy performed. It is important that the patient has demonstrated his ability to give up smoking before considering the operation. Whiskey, papaverine and aspirin are vasodilating drugs of some aid. That this conservative type of therapy will be effective in most instances is shown by the amputation incidence at Post-

Graduate Hospital (Table IV); of twenty-two in 18,500 visits of diabetics to the clinic (.0011 per cent) and twenty-two in 1,160 admissions of diabetics to the hospital (.018 per cent).

Local infection once present is difficult to eliminate. In addition, occlusion of local vessels may cause tendon or muscle sloughs. Local amputations of toes may then be required. Wire sutures are placed but not tied in this type of amputation. Where several toes are involved we are interested again in the metatarsal amputation with solar flap, again not closed as discussed by McKittrick. Many of these will heal provided no closure is done and we are proximal to the area of slough. Sterile daily soaks aid healing by removing any collections in the wound. Again let me emphasize that any part of the patient's own foot that he can stand on is better than the most perfect prosthesis.

There are published results on below-knee amputations and their value in rehabilitation. We do not do many below-knee amputations. I believe we save part of the foot in many that others would amputate below the knee. Where spreading infection or gangrene dictates an amputation it is safer above the knee due both to distance from the infection and better blood supply. Once the femoral artery divides, the branches are extremely small. When infection is spreading there comes a time when the decision for operation must be immediate. It is wise to prepare the patient and family for such a possible decision so that there will be no delay at that time.

There is a safe period during which the diabetic can stand a major amputation. If this optimal time passes, like the optimal time for goitre surgery after iodine preparation, it cannot be regained.

Pre-operative preparation should include attention to diabetic control, chemotherapy and adequate local cleansing. The gas forming organisms can be eliminated if the chemotherapy and local cleansing are combined. *Clostridium welchii* and *Bacillus perfringens* inhabit the colons of elderly individuals. As these patients are bed ridden, these organisms may be rubbed into the skin. To eliminate them we use three individual skin washings prior to operation. The first scrubbing stimulates the sebaceous glands to secrete and the other ones wash off any organisms thus liberated. In one early case of gas bacillus death we were able later to culture the organism from the skin below the amputation site. Penicillin and prophylactic gas gangrene serum should be used.

After considerable experience we now employ refrigeration anes-

TABLE V—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

<i>Anesthesia used in Diabetic Amputation</i>	
Cyclopropane	20
Refrigeration	16
Local	3
Spinal	1

thesia in all our major amputations (Table V). The technique modified from that of Allen and Crossman consists of introduction of the limb into the icebox for one hour, application of a tourniquet and return to the icebox for one and one-half hours. Operation can then be performed without further anesthesia or without pain provided the sciatic nerve is anesthetized locally before division. This should be done in all anesthetics, as sectioning of the sciatic nerve can cause shock. In one instance the blood pressure dropped to 0 when the sciatic was divided under nitrous oxide without previous novocaine infiltration. In some, out of diabetic control, the tourniquet performs the functions of amputation; the temperature drops, with no further absorption and diabetic control may be obtained. In these, amputation may be postponed many hours to a safer period. The amputation technique consists of a circular incision at the level of the patella with division of the muscles one inch above the skin edge where they are mostly tendinous and division of the femur directly above the condyles. No muscle or fascial flaps are made and the stump is closed by three or four steel wire sutures through the skin only. No drain is necessary as there is adequate drainage opening between the sutures. The periosteum is not removed from the femur as this periosteal excision may cause a bone necrosis. In some, sulfa powder is applied locally. The wound is dressed and immediate traction applied by weights on a stockinette. The nerve end is treated by simple ligation and severance with a sharp scalpel one-half inch distal to the suture. Phantom limb pain has been no more common with this simple method than after alcohol injections or plastic operations on the nerve. In our experience phantom limb is best treated by forgetting it. Phantom limb is natural after amputation but phantom limb pain is abnormal. Phantom

limb pain is a contagious lesion and one often can prevent its appearance by not suggesting it. On one Navy hospital ship load from Saipan every one of twelve amputees had phantom limb pain. When we questioned the amputees, we found that one of them had a brother who had had phantom limb pain and had told his brother about it. I recall no other phantom limb pain that early in all of the Marine and Navy casualties I saw. Postoperatively the diabetes is watched carefully.

The patient should be out of bed immediately after the operation to reduce complications. We place them in a chair the same day. We cover the stump with oil silk to prevent contamination. The splint permits early movement. Even when weights are applied the patient may be in a chair. The wound is not dressed, unless fever requires it, for ten days. We have had 88.8 per cent primary unions by this technique in contrast to 20 per cent previously. The pre-operative diet and insulin are started at once and if not tolerated, replaced by intravenous feedings. Again, the patient is permitted to run a small amount of sugar until he is stabilized.

One of the most important parts of our service to the diabetic amputee now begins. With the coöperation of the physiotherapy, internal medicine and social service departments we begin rehabilitation at once. The patient is taught to use crutches and to go to the bathroom immediately. Even elderly individuals will learn to use crutches provided they are started early in walkers. Where amputation has appeared inevitable, arm and shoulder exercises have been developed before operations. The patient begins to look forward eagerly to the physiotherapist's visit and we are able with very few exceptions to have these patients walking on crutches when they leave the hospital. This makes them independent and gives them an ambition for an artificial limb. In my experience the diabetic who is relegated to a bed or wheelchair soon dies. I cannot over-emphasize the change this rehabilitation program has made in our amputees. The Social Service contacts the employers and friends and where possible resumption of work, even at home, is started, frequently with the use of other amputees to show the progress that can be made. We encourage the early application of an artificial limb.

Until such time as we are able to control the various factors that cause arterial degeneration, this problem of amputation will be with us. No gadget or mechanical marvel apparatus will be the answer. Careful

TABLE VI—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service

<i>100 Major Amputations for Vascular Disease</i>			
Diabetes	40	Deaths	4
Arteriosclerosis	38	Deaths	2
Thrombo-angiitis obliterans	4	Deaths	0
Embolic	6	Deaths	4

TABLE VII—NEW YORK POST-GRADUATE HOSPITAL
Vascular Surgery Service
Deaths After Amputation for Diabetic Gangrene—1940-1945

<i>Sex</i>	<i>Age</i>	<i>Time of Death</i>	<i>Cause</i>
1. Male	72	6 weeks after operation	Cerebral thrombosis
2. Male	74	Survived guillotine amputation Died 4 weeks after revision	Shock
3. Female	57	7 weeks after operation	Ascending gangrene of stump into buttocks and abdomen
4. Female	62	7 days	Infection; refused operation for one month

common sense and conservative measures will help many permanently and the rest until such time as the life of the part is lost and the infection is becoming uncontrollable. Immediate and adequate surgery then will result in the highest percentage of viable patients. The patient who can be taught "to live with his disease and in spite of it with the help of a careful physician will outlive perhaps his undiseased fellow men."

To know one's physical shortcomings makes possible preparation in advance to combat the eventual complication stage. If I may quote again "diabetes is a good disease itself, it just keeps bad company." We must guard against this bad company.

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THE INAUGURATION OF THE
SECTION ON MICROBIOLOGY

GEORGE BAEHR, *President, The New York Academy of Medicine*

THE establishment of a Section on Microbiology represents an important departure from the Academy's tradition. I deem it, therefore, a great privilege to be invited to address the members at this first meeting of the Section. During the first seven years after the founding of the Academy in 1847, its work was carried on through a number of standing committees of Fellows, who concerned themselves with studies and reports upon the burning scientific, clinical and public health questions of the day. The reports of these committees were presented at the Stated Meetings at which, occasionally an essayist from the Academy's Fellowship or a guest from another city would also read a formal paper on some new or controversial subject such as the value of anaesthesia which had been introduced in Boston in 1846 or the revelations of the microscope. In the absence of exact knowledge concerning the cause and nature of infections during those early days, the heated discussions on debatable subjects such as this often aroused prolonged and even bitter controversy among the Fellowship, which were sometimes resumed at a succession of monthly meetings with remarkable tenacity.

By 1854 the growth of the Academy's Fellowship and the failure of some of the committees to function adequately enabled Dr. James Anderson to persuade the Academy to revise its Constitution and By-Laws for the purpose of subdividing the Academy into Sections related to the various clinical and other branches of medicine. Some of the sections were established, therefore, ninety-three years ago. During the past generation standing committees on the library, public health relations, medical education and public medical information have carried on the broader basic responsibilities of the Academy under its charter. But the monthly activities of the eleven, now twelve Sections and of the affiliated societies comprise the actual clinical and scientific life of the Academy.

Until today, all Sections were devoted to clinical medicine, surgery or the various specialties, with the one exception of the Section on Historical and Cultural Medicine. There were several reasons why the officers and council of the Academy were reluctant heretofore to encourage the establishment of Sections dealing with the basic medical sciences. It was feared that they might discourage the presentation of scientific work before the ten clinical Sections which serve as channels for the dissemination of new clinical and scientific information to the physicians of the city and its environs. The officers and council of the Academy also wished to avoid a conflict in interest with the affiliated scientific societies which meet regularly in this building, such as the Society of Experimental Biology and Medicine and the New York Pathological Society.

We are indebted to your chairman Dr. Gregory Shwartzman, and the members of the organizing committee, for convincing the officers and council of the necessity for abandoning our ancient restrictions. I did not need much persuasion for I have long felt that the rapid expansion of our scientific horizons had made it desirable to establish one or more Sections devoted specifically to the basic medical sciences. This is especially true of microbiology which represents a composite field of several overlapping laboratory disciplines but which does not duplicate the essential interests of our affiliated societies. I can foresee the need for at least one other new Section sometime in the future devoted perhaps to the Physical and Chemical Sciences related to Medicine. Its establishment may soon be justified by the phenomenal pace at which these fields of science have grown, especially during and since the War and by their increasing importance for scientific investigation and even for routine clinical diagnosis and therapy. Biophysics, like biochemistry is related to all clinical fields and its technology is expanding so rapidly that it will soon require a place where its experts can assemble and exchange experiences among themselves and among the clinical and scientific workers enrolled in the present Sections of the Academy.

The New York Academy of Medicine is, as you well know, one of the medical cultural centers of this country. Its library is one of the greatest depositories of medical literature in the world. Like its library, the meetings of its various Sections and affiliated societies are open to the medical profession on almost every day in the week. On some eve-

nings as many as five such meetings are held in this building simultaneously. On behalf of the officers and council of the Academy, I take pleasure tonight in welcoming this new venture into our Fellowship. Aside from the many new scientific contributions in microbiology which will be reported at your monthly meetings, I am confident that another of the benefits to the Fellowship of the Academy will come from the effects of your cross-fertilization upon the scientific proceedings of the other eleven Sections and upon the basic work of the Academy in the fields of public health and medical education.

SECTION ON MICROBIOLOGY

NOVEMBER 25, 1947

I. OPENING ADDRESS

ORGANIZATION OF THE SECTION ON MICROBIOLOGY

George Baehr, *President, The New York Academy of Medicine*

II. SCOPE OF SECTION ON MICROBIOLOGY

Gregory Shwartzman, *Chairman, Section on Microbiology*

III. PAPERS OF THE EVENING

a. Bacteriological aspects of tuberculosis

Rene J. Dubos, Ph.D., Rockefeller Institute for Medical Research

b. Anti-microbial therapy of tuberculosis: The significance of finding of tubercle bacilli resistant to streptomycin in vitro

Walsh McDermott, New York Hospital

c. Modifications of tuberculous lesions in patients treated with streptomycin

John G. Kidd, Cornell University Medical College

IV. DISCUSSION

To be opened by J. Burns Amberson, Bellevue Hospital

Gregory Shwartzman
Chairman

The Mount Sinai Hospital

Harry Most
Secretary

New York University
College of Medicine

*Scope of Section on Microbiology**GREGORY SHWARTZMAN, Chairman, Section on Microbiology*

I would like to begin the outline of the scope by stating that all members of the organizing group, namely, Drs. R. J. Dubos, F. L. Horsfall, Jr., J. G. Kidd, C. M. McLeod, H. Most, R. S. Muckensuss and myself participated jointly and equally in the organization of the Section on Microbiology.

The task has been indeed a pleasant one due to the interest, encouragement and aid rendered to us by the Officers and the Council of the Academy. In particular, Drs. George Baehr, Waldo B. Farnum, Howard Reid Craig and Mahlon Ashford devoted much time to guide our initial steps.

Our sponsors who petitioned the Council to form this Section have been most generous in their support. The sponsorship by outstanding representatives of various fields of laboratory and clinical sciences affords the opportunity of organizing our work along broad lines dictated by the present-day needs, as we see them.

At the present stage of scientific development, we are confronted with two trends, seemingly opposing each other. Rapid progress necessitates specialization and concentrated efforts in limited fields. On the other hand, there is a continuous widening of the scope and ever-growing alliance of microbiology with other sciences, for mutual benefits.

For instance, some twenty-five years ago investigators dared not compare bacterial chemistry with that of animal cells. It would have been heresy to assume a similarity between the substances supporting bacterial growth and vitamins supporting growth of animal cells. Now we realize how closely related are the problems of bacterial and animal cell nutrition. As a matter of fact, appreciation of this relationship has been greatly responsible for some recent discoveries of vitamins of considerable importance in human nutrition.

Problems of general biology as important as those concerned with the nature of life have confronted the microbiologist investigating the nature of viruses.

The geneticist has enriched microbiology with ideas of genetic dissociation and, by the same token, supplied this science, as well as biochemistry, with new tools for the studies of cellular metabolism. In exchange, immunochemical investigations on type specificity of certain bacteria have unexpectedly assumed significance in genetics since they may aid in the identification of chemical agents involved in hereditary transmission of cellular characteristics.

The botanist and mycologist had long stood in isolation in their preoccupation with the classification of thousands of species of molds. However, the thankless and heroic task of classification has become most valuable when some seemingly useless molds proved to be great human benefactors.

Discoveries of chemotherapeutic agents made by the chemist played havoc with accepted ideas of immunology concerned with specific serum therapy and prophylaxis of certain diseases; while discoveries of antibacterial agents originating from bacteria and molds made by the microbiologist have challenged the skill of the organic chemist in chemical synthesis.

One could go on with examples of this sort, all serving to emphasize that it is most essential for the investigators in biological and medical sciences to be aware of each others problems, and above all, to look for correlation of rapidly accumulating new observations.

Due to its broad interests, The New York Academy of Medicine is best suited to provide a forum for exchange of information between allied groups of investigators. The scope of the new Section must be clearly defined but sufficiently broad in order to serve both the microbiologist and the scientists in allied fields.

The fields of interest to the Section will be bacteriology, mycology and parasitology; viruses and rickettsiae; maladies of unknown and uncertain etiology, possibly of infectious origin; immunology; chemother-

apy; pathology relative to microbiology; and methods of study adopted from related sciences, as applied to microbiology.

Our meetings will be preferably devoted to various aspects of single topics in the form of evening sessions and, from time to time, in the form of more extensive symposia.

Fellows of the Academy interested in the work of the new Section are cordially in-

vited to enroll as its members. The meetings will be open, however, to all interested.

Tonight's session will deal with bacteriological, chemotherapeutic, and pathological aspects of tuberculosis.

We are happy to have Dr. Rene J. Dubos, one of the most outstanding microbiologists, to present the first paper of the first session, the paper on bacteriological aspects of tuberculosis.

Bacteriological Aspects of Tuberculosis*

RENE J. DUBOS, PH.D.

The Rockefeller Institute for Medical Research

In contrast to other living cells tubercle bacilli are not readily wetted by aqueous solutions in the usual bacteriological media. As their surface is strongly hydrophobic and lipophilic, the bacilli tend to grow in the form of clumps or pellicles instead of being dispersed throughout the aqueous phase. In addition to being the source of technical difficulties, this mode of growth gives rise to cultures consisting of heterogeneous cell populations. It has been found that a certain wetting agent (a water soluble ester of long-chain fatty acid, known under the name of Tween) has the property of wetting the surface of the bacillus and of permitting dispersed homogeneous growth. The use of this substance in culture media has led to the following findings:

Long chain fatty acids constitute a favorable source of carbon and energy for the growth of tubercle bacilli; other tissue substances (as yet unidentified) can also greatly stimulate the rate of growth. Serum albumin protects the bacilli from the toxic action of many substances which often contaminate bacteriological media. These observations may lead to the development of more rapid and effective techniques for the bacteriological diagnosis of tuberculosis.

The susceptibility of tubercle bacilli to

certain antibacterial agents—to penicillin for example—is much increased when the wetting substance, Tween, is added to the test medium. This suggests that the resistance of these organisms may be due in part to the fact that the usual chemotherapeutic agents cannot normally reach the susceptible cellular structure of the bacterium.

Dispersed cultures are very convenient for the production of experimental infections. Inoculation of mice with cultures growing in the dispersed state has led to the following observations:

Mice of different genetic backgrounds exhibit great differences in susceptibility to tuberculous infection.

For any given mouse strain, the rate of development and outcome of the disease is markedly affected by environmental factors; in particular, by the state of nutrition and by other concomitant pulmonary infections caused by filtrable viruses.

The virulence of different cultures of tubercle bacilli for mice (and for other animals) is correlated with marked differences in the morphological and immunological characteristics of the bacilli. It is hoped that the chemical identification of the factors responsible for these differences may lead to a better understanding of the nature of virulence and to a more rational approach to the problem of immunization.

* A complete paper will appear in this *Bulletin* at a later date.

The Significance of the Finding of Tubercl Bacilli Resistant to Streptomycin in Vitro in the Anti-Microbial Therapy of Tuberculosis

WALSH McDERMOTT

The New York Hospital, New York

In tuberculosis, as in other infections, when the administration of streptomycin is continued for a sufficient period, to patients with untreated lesions which continue to discharge bacteria, cultures of the obtainable bacteria will grow abundantly in vitro in the presence of high concentrations of the drug. This phenomenon is designated "the emergence" or "the appearance" of "bacterial resistance," and the term "streptomycin-resistant" is used to designate cultures of tubercle bacilli which grow readily in vitro despite the presence of 100 micrograms of streptomycin per cc. of medium. It should be noted that the data to be presented should not be applied to meningeal tuberculosis which is treated with high concentrations of streptomycin administered by the intrathecal route.

The speed with which bacterial resistance appears varies considerably, depending upon the species of the infecting microorganisms. In the series of approximately 100 tuberculous patients which Dr. Muschenheim and I have been studying for the past two years, the earliest detection of drug-resistant cultures was after five weeks of streptomycin therapy. In general, however, the initial appearance of the phenomenon was detected between the sixtieth and the ninetieth day of treatment.

If drug-resistance demonstrable in vitro reflects the presence of a drug-resistant infection, it follows that the total period during which streptomycin might be of value would usually be limited to only one to three months. There has been some reluctance to accept the notion that tubercle bacilli which are drug-resistant in vitro, are similarly drug-resistant in the patient.

One observation which leads some to skepticism is the fact that in certain pa-

tients the first conspicuous roentgenologic improvement has been observed during the third and fourth months of streptomycin therapy at a time when the cultures obtained from the patient are streptomycin-resistant.

Another reason for questioning the significance of the finding of drug-resistant cultures is the fear that the conditions of in vitro testing could be such that a culture containing only a small percentage of drug-resistant cells would falsely appear predominantly or uniformly resistant.

Obviously, the validity of the latter objection would depend upon the conditions of the in vitro testing. The particular test used in our own studies is a serial dilution method in which the albumin-Tween medium of Dubos and Davis is used.

Examination of the material from the clinical study, in which this test was used, provides evidence for proper consideration of these questions.

The course under continued streptomycin therapy of patients with hematogenous or pulmonary infections who continue to discharge drug-resistant bacilli was presented. On the basis of these observations, it was concluded:

1) The continued administration of streptomycin to patients who continue to discharge tubercle bacilli results in the emergence of bacterial resistance usually within sixty to ninety days of the start of the antimicrobial therapy.

2) In generalized hematogenous tuberculosis, it appears certain, and in pulmonary tuberculosis, highly probable, that the emergence of streptomycin-resistant organisms (under the conditions of the test employed) indicates the presence of an infection which is drug-resistant in the patient.

*Modifications of Tuberculous Lesions in Patients Treated With Streptomycin**

JOHN G. KIDD

The New York Hospital, Cornell Medical Center

During the past year seven patients who had been given streptomycin in the treatment of miliary tuberculosis have been examined postmortem in the Department of Pathology of The New York Hospital—Cornell Medical Center. In all of these cases there was evidence that the tuberculous lesions had been modified by the therapy.¹

In one patient, for example, extensive miliary tuberculosis of the lungs, demonstrated roentgenologically, had resolved completely after about thirty-five days of therapy, while an associated tuberculous meningitis at first had responded to the drug given intrathecally but eventually had relapsed, causing an internal hydrocephalus and death 297 days after the initial diagnosis had been made. Gross examination of the lungs postmortem revealed no trace of miliary lesions, and cultures of the lungs for acid-fast bacteria were negative, though a healed primary complex was found. Microscopically, there were many small scars consisting of loose fibrous tissue scattered irregularly throughout all lobes of the lungs; these revealed no evidence of active tuberculosis, and they were interpreted as being the healed remains of miliary nodules (Figure 1).

In still another patient, miliary tubercles of the lungs had disappeared following the initiation of drug therapy, as indicated by x-ray examinations, and a tuberculous lymphadenitis had subsided notably. The miliary tubercles reappeared, however, and the lymph nodes enlarged again some weeks later in spite of continued chemotherapy, and during this relapse tubercle bacilli isolated from a cervical node proved markedly resistant to the effects of streptomycin,

growing in the presence of 1000 units of the drug per cc. of medium, whereas those that had been isolated prior to treatment were inhibited by a concentration of 1.5 units per cc. On postmortem examination very many large miliary tubercles were visible in the lungs; these were discrete, spherical, and about five times the size of the usual hard miliary tubercles; microscopically each tubercle was composed of a thick fibrous capsule arranged concentrically about an area of caseation and granulomatous inflammation that often had broken through the fibrous barrier and more or less surrounded the latter (Figure 2). These lesions contained great numbers of acid-fast rods, as special stains revealed, and their "inside-out" character made it seem that the disease process had been held in check for a time and then gained overwhelming impetus, perhaps when bacterial variants resistant to streptomycin had become prevalent in the lesions.

Focal scars similar to those already described were seen in the lungs of the remaining five patients, all of whom had responded temporarily to the drug therapy, though in four of these cases active tuberculosis was more or less widespread throughout the lungs or in the central nervous system in addition; often healed lesions and active ones were present side by side in the same microscopic field. In every case where the scars of healed miliary tubercles were found in the lungs they were likewise present in other viscera, notably in the liver, spleen, and kidneys. There was also evidence, both clinical and anatomical, of healing of tuberculous meningitis in three of the cases, yet it is noteworthy that the meningeal process was more or less active at the time of death in six of the seven patients. As previously reported,¹ the anatomical findings in general were quite similar to those noted by Baggenstoss, Feldman, and Hinshaw in

* Read November 25, 1947 before the first meeting of the Section on Microbiology of The New York Academy of Medicine.

From the Department of Pathology, The New York Hospital—Cornell Medical Center.



Figure 1. The scar of a healed miliary tubercle in the lung in a case of streptomycin-treated tuberculosis (Case No. 1—12164). Small scars such as this, scattered irregularly throughout all lobes of the lungs, were the sole remains of an extensive miliary tuberculosis in this case. Similar areas of focal fibrosis were found in the lungs in all of the 7 cases here reported.

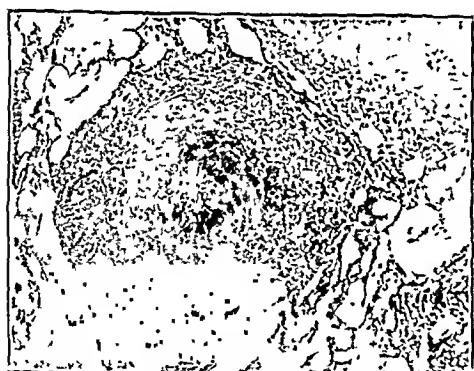


Figure 2. An "inside-out" tubercle, great numbers of which were present in the lungs of Case No. 3—12092. These modified tubercles are much larger than ordinary hard tubercles and are composed of a partially caseous center surrounded by a thick rind of fibrous tissue through which the active process has extended to form a broad outer layer of tuberculous inflammatory tissue. It is noteworthy that acid-fast bacilli, presumably markedly resistant to streptomycin (see text), were present in great numbers in these lesions, both in the outer inflammatory zones and in the caseating centers.

five cases of miliary tuberculosis that had been similarly treated with streptomycin.²

The fact deserves special emphasis that in five of the seven patients the tubercle bacilli isolated some days or weeks after streptomycin therapy had been instituted and during a period of relapse were markedly resistant to the action of streptomycin, often growing uninhibited in the presence of 100 to 500 units of streptomycin per cc. of culture medium, whereas the bacilli that had been isolated prior to treatment in every case had failed to grow in media containing 2 units or less per cc. In four of these cases a close correlation could be made between the clinical remission followed by relapse, the presence in the lungs or in the central nervous system of older healed lesions and newer active ones, and the manifestation of drug-fastness by the bacilli isolated in the terminal stages of the disease.

From a consideration of the findings as a whole, it seems plain that streptomycin therapy may greatly modify the character of the lesions in miliary tuberculosis, and the inference seems warranted that the disease process may often be largely overcome by the combined influences of the drug and the body's defences, only to "light up" later when drug-fast microorganisms become dominant in the lesions. In addition, the postmortem studies have disclosed the pathogenesis of another limitation in the use of this drug. For five of the patients in the group had become partially deaf as a result of its toxic action, and several exhibited marked vestibular dysfunction as well; all of these patients showed degenerative changes in the neuroges of the 8th cranial nerve nuclei, the cellular abnormalities ranging from an hydropic degeneration of cytoplasm to complete liquefaction necrosis, while similar changes were found in the ventral cochlear nuclei of three dogs given massive doses of streptomycin experimentally.³

* * * *

It is of course gratifying to the pathologist to be able to bring anatomical findings such as these into close apposition on the one hand with the natural history of a disease process, as portrayed here by the

precise observations of my clinical colleagues, and on the other hand with etiological factors, as exemplified in these cases by the detailed studies of the infecting microorganism made in the laboratory of my distinguished predecessor on this evening's program; for such is one of the main functions of the pathologist. But the essential facts of these studies may be viewed with pleasure also in a much larger frame of reference. For nowadays the anatomy of infectious disease processes is notably different to what it was only a few years ago, thanks to the widespread use of the sulfonamides, penicillin, and the newer antimicrobial agents. For example, Hugh Cairns and Dorothy Russell have recently described proliferative and necrotizing cerebral arteritis and phlebitis in cases of pneumococcal meningitis that survived 7 weeks or longer under treatment with penicillin, the lesions having not been seen in prechemotherapeutic days when death from this disease invariably occurred within a week or two.⁴ And everyone who reviews large numbers of postmortem examinations has, I am certain, been impressed with the relative paucity of the infectious lesions that now pass under his eye. To cite in general terms a part of our own experience in this relation I may say that we have not had a case of pneumococcal lobar pneumonia on the necropsy service of The New York Hospital—Cornell Medical Center during the past four years and the number of clinically-significant bronchopneumonias due to pneumococci, streptococci, and staphylococci has sharply

diminished, while those now appearing are often milder, with more resolution and less inflammation than used to be seen in such cases. If the effectiveness of our armamentarium against infectious diseases continues to increase during the next few years as it has in the past decade—and the new Section on Microbiology of The New York Academy of Medicine is largely dedicated to this end—we may look forward to the day when the pathologist will no longer see infectious disease processes at all, except when he chooses to create and study them in the experimental animal for his further enlightenment. Soon may that day dawn!

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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MARCH 1948

RENAL TUBULE WORK:
ITS SIGNIFICANCE FOR THE CLINICIAN*

L. H. NEWBURGH

Professor of Clinical Investigation, The Medical School, University of Michigan

I t has become securely established that the body cells are immersed in a fluid characterized by a nearly fixed composition; that protein free plasma and interstitial fluid are essentially identical and are the two interchanging portions of the extracellular fluid; that the constancy of composition of this fluid is maintained by the activity of the kidneys; that the walls of the glomerular capillaries are filters which permit the passage through them of everything in solution other than the protein.

By definition, filtration is a passive process in so far as the filter is concerned and takes place solely because the fluid pressure on one side of the membrane is greater than on the other side of it. The concentration of a filterable substance is the same on both sides of the filter.

Homer Smith¹ and his collaborators have demonstrated that, about 180 liters of glomerular filtrate are produced each 24 hours by healthy adult kidneys. Since this strikingly large volume of fluid has practically the same composition as the extracellular fluid, each liter of it contains,

* Given April 15, 1947, before the Centennial Meeting, Section of Medicine, The New York Academy of Medicine.

for example, approximately one gram of glucose and a third of a gram of urea.

If the lining membrane of the tubules through which this fluid is flowing was passive in the sense that the walls of the glomerular capillaries are, the urine would have the same composition as the filtrate. But this is not at all the case, for as is well known, the glucose has disappeared and the concentration of urea has increased 50 to 100 fold. These changes are brought about by the activity of the tubular epithelium. These cells do work and it is this feature of renal physiology to which I want to direct your attention.

Von Rhorer² as long ago as 1905, showed that this kind of work can be calculated* for any urinary constituent when one knows the concentration of the substance on each side of the membrane and the amount of the substance accumulated in the urine. The equation shows that when the concentrations of a substance in the plasma and the urine are the same, no work has been done regardless of the amount of the substance excreted. But as these concentrations diverge, more and more work has been required per unit of substance to establish the widening difference. Likewise, given any two concentrations that are fixed but different, more work has been done to establish this difference when a large amount of the substance is involved than when only a small amount is acted upon.

Some substances are more concentrated in the urine than in the blood while the concentration of other entities is greater in the blood than in the urine. Urea is an example of the first group. Its concentration in the urine is commonly 100 times that of the blood. Glucose is the outstanding member of the other group since its concentration in the plasma is several hundred times that of the urine. Furthermore it should be emphasized that the ions of sodium and chlorine whose concentration in the plasma is nearly constant in health are under some circumstances more concentrated and under other circumstances less concentrated in the urine than in the plasma. These latter situations may

* The work for any single urinary constituent is calculated by means of the following equation:

$$\text{Work} = NRT \times \left\{ 2.3 \log \frac{U}{B} \frac{U-B}{U} \right\}$$

where N is the number of mols of the substance; R is the gas constant — (1.987 gram calories per °C). T is the absolute temperature ($37^\circ\text{C} + 273^\circ\text{C} = 310^\circ\text{C}$). U is the urinary and B , the plasma concentration of the substance.

The term "Work" as employed here is the useful work. If the efficiency of the operation is 100 per cent, it is also total work.

For a discussion of the derivation of the equation and its application to renal physiology see J. D. Newburgh, The changes which alter renal osmotic work, *J. Clin. Investigation*, 1943, 22:439.

be exemplified by describing certain events in a normal man. His plasma contains 3.3 grams of sodium per liter. If his habitual diet contains this same amount of sodium, he will excrete 3.3 grams of sodium in the urine each twenty-four hours (disregarding the small losses through skin and in the feces). And if the volume of urine is one liter, the concentration of sodium in it will be the same as that of the plasma. Hence no work has been required to keep the plasma sodium at its normal value. Simple diffusion sufficed. Next, the urine is set at two liters without change in sodium intake. The 3.3 grams of urinary sodium will now be distributed through two liters, and therefore its concentration per liter will be half that of the plasma. This difference has been brought about by the work of the tubule cells which have caused sodium to move from a region of lower to one of higher concentration. In a third hypothetical situation, the urine volume is one liter again but the sodium intake is 6.6 grams daily instead of the previous 3.3 grams. When balance is attained, the urine will contain 6.6 grams per twenty-four hours and so its concentration will be twice that of the plasma. But now the work has caused the urine to become more concentrated than the plasma whereas in the previous setup the concentrations were the other way round. So these remarkable tubule cells can cause the urinary sodium to become either more or less concentrated than it is in the plasma, whichever direction guards the fixity of the plasma value.

The excretion of urea presents several interesting contrasts to what has just been said regarding sodium. Urea is always more concentrated in the urine than in the plasma. Accordingly its excretion always requires work, and increase in urine volume always lessens the work for the same amount of urea. But with the usual amounts of salt in the diet, increasing urine volume beyond a liter or 1500 cc. demands progressively larger amounts of work to keep the plasma sodium at its normal level. Accordingly calculation of the total work for urea, sodium and chlorine brings out the point that there is a urine volume at which this combined work attains its least value.

Figure 1 presents some calculations of work that demonstrate these relationships. It is seen that with a fixed concentration of plasma urea, the excretion of 15 grams of urea in one liter of urine requires about 60 units of work, but that the same total amount of urea distributed through two liters of urine reduces the work to 40 units and further dilution requires still less work. This is the effect of reducing the ratio

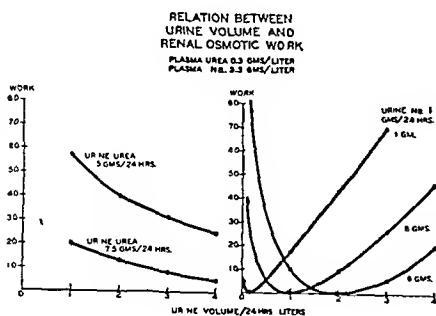


Figure 1

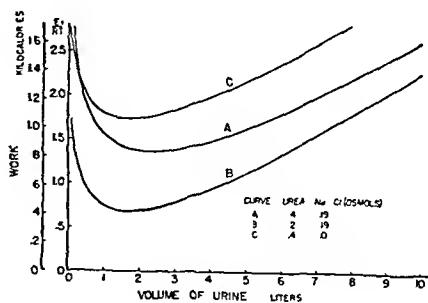


Figure 3

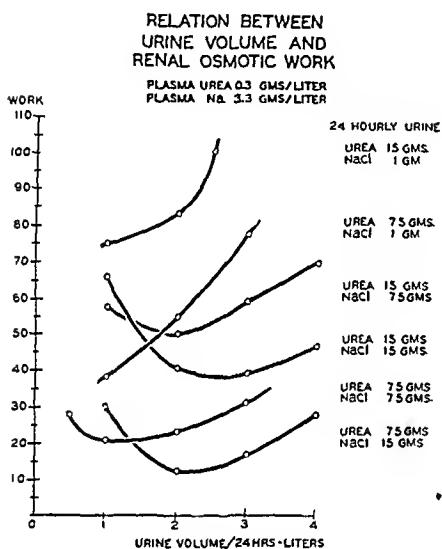


Figure 2

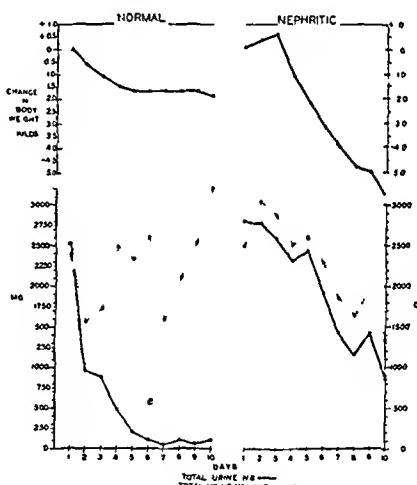


Figure 4

of the concentrations of urine to blood urea from 50 to 25 to 17 when the total amount of urea excreted is always 15 grams.

But work is related not only to difference in concentration of a substance on the two sides of the barrier but also to the amount of the substance transported. This second factor may be evaluated by comparing the excretion of 15 grams of urea in 2 liters of urine with the excretion of 7.5 grams of urea in one liter of urine. Under these circumstances the ratios are the same in the two cases, but the work required to excrete the 15 grams of urea is 40 units as compared with only 20 units for the smaller amount of urea.

Turning now to sodium and chlorine, it is seen that there is a urine

volume at which no work is done and that either increase or decrease in volume is accompanied by work. Thus, the excretion of 16 grams of NaCl in 2 liters of urine is accomplished without work because the plasma and urine concentrations of the substance are the same; but when the volume of urine is either less or greater than 2 liters, work must be done since in both cases a difference in concentrations in plasma and urine has come about. For example, the concentration of 16 grams of NaCl in one liter of urine is twice that of the plasma whereas the distribution of the 16 grams in 3 liters reduces the urinary concentration to two-thirds that of the plasma. It will be seen also that when low sodium diets are administered, the work requirement is considerable even at one liter of urine, and that it rises sharply as volume of urine increases. Accordingly, the progressive reduction of work for urea obtained by increasing urine volume may be counterbalanced by the adverse effect of large urine volumes on the work required to return the NaCl from the glomerular filtrate to the plasma.

Figure 2 displays these relationships. The curves show the total work required to excrete urea and to maintain the normal plasma concentration of Na and Cl. It will be seen that the work is greatest at every urine volume when dietary sodium chloride is one gram even though the dietary protein is within the normal range. The least work is required when the diet is low in protein and high in salt, and the urine volume is at two liters. It is seen further that increasing its volume beyond this amount augments work somewhat, and that a reduction to one liter doubles the work.

Figure 3. The work for each constituent in a normal 24 hourly urine was calculated and the sum of all of these values is represented by curve B. Doubling the urea without change in the other urinary constituents gives Curve A. The increased work at all urine volumes is evident. Curve C is based on the same urine as Curve A except that it contains no NaCl. Inspection of these curves brings out the interesting fact that the least work is required when the volume of urine is about 2 liters regardless of whether the diet is high or low in protein or salt; and that the work increases sharply as the volume of the 24 hourly urine falls below one liter.

Addis³ has calculated the work performed in the excretion of the urea resulting from low and high protein diets. When the subjects were healthy young men he obtained the responses shown in Table I.

TABLE I
WORK FOR EXCRETION OF UREA. LOW AND HIGH
PROTEIN DIETS. HEALTHY YOUNG MEN.

<i>Protein gms./24 hours</i>	<i>Urine volume cc./24 hours</i>	<i>Work gram cal.</i>
40	1219	499
120	1222	1155
200	1415	1775

TABLE II
EXCRETION OF SMALL AND LARGE AMOUNTS OF UREA

<i>Urea mg./24 hrs.</i>	<i>Concentration of Urea Plasma mg. per cent</i>	<i>Urine mg. per cent</i>	<i>Ratio Urine Plasma</i>	<i>Work per gm. kidney protein gram cal.</i>	<i>Total gram cal.</i>
360	35	6125	170	95	16
1080	67	8934	120	225	44

ADJUSTMENTS TO REDUCTION OF KIDNEY MASS

<i>Urea mg./24 hr.</i>	<i>Concentration of Urea Plasma mg. per cent</i>	<i>Urine mg. per cent</i>	<i>Ratio Urine Plasma</i>	<i>Work per gm. kidney protein gram cal.</i>	<i>Total gram cal.</i>	<i>Amount of Kidney Excised per cent</i>
360	35	6125	170	95	16	0
360	44	4284	97	99	14	25
360	66	3192	48	107	11	75
1080	67	8937	120	225	44	0
1080	144	4538	32	222	23	75

These data show that the work done by normal tubule cells increases with the load and that the very large amount of urea derived from the 200 grams of protein is excreted almost without employing the device of increased urine volume.

The adjustments that take place when the excretory mechanism is

presented first with a moderate and then with a very large amount of urea, are seen in more detail in the next table. Addis³ obtained the data from two groups of rats, one of which received a diet that yielded three times as much urea as the other one. It is seen that a trebling of the load is accompanied by a nearly threefold increase in work. But still more work would have been required if two other shifts had not taken place, namely, the increased concentration of urea in the plasma and the large increase in urine volume. These two shifts reduced the ratio of the concentrations of urine urea to plasma urea from 170 to 120.

Further studies by Addis dealt with the adjustments to reduction in the amount of functioning kidney tissue (Table II). Now the largest change consists in a lessening of the ratio—urine to plasma concentration of urea. The increase in plasma level is simply the resultant of lessened volume of glomerular filtrate caused by excision of portions of the kidneys. Since, as less urea is filtered in a unit of time, more will accumulate in the blood until the concentration of plasma urea is great enough to restore the original rate of passage through the diminished area of filter. The second important adjustment is the great increase in urine volume. It will be seen that the work per unit of remaining kidney does not increase. This might indicate that the tubule cells could do no more work. But this is certainly not the correct explanation since when the urea load is trebled work does go up from 100 to 220 even though in both cases 75 per cent of the kidneys has been excised.

Regarded clinically it may be very significant that more work is done when the diet is high in protein than when it is low. I refer to the ancient and widely accepted dictum that directs the physician to lessen the work of the diseased organ. The experiments just described indicate that this can be accomplished by feeding the smallest amount of protein that will maintain nitrogen balance.

Addis has investigated this question. He found that rats whose kidneys had been reduced to one-fourth their original size and who were then given an 18 per cent protein diet, developed the cardinal signs of advanced glomerular nephritis. Then some of these nephritic rats were shifted to a diet containing only 5 per cent of protein and others were placed on a very high protein diet. The former showed considerable improvement whereas in the latter animals the renal

disease grew worse in all respects. When rats were placed on the low and high protein diets respectively immediately after the excision of three-fourths of the kidneys, all the animals that received the high protein diet died, while all those given the low protein diet survived.

Perhaps even more significant is the experimental work of Farr and Smadel.⁴ They succeeded in producing an experimental nephritis that closely resembles human glomerular nephritis by injection of an anti-kidney serum. And they showed that the course of this disease is influenced to a striking degree by the amount of protein in the diet. Rats tended to recover promptly from the nephritis when their diets contained only 5 per cent of protein. In animals that were fed 18 per cent of protein, the disease became chronic and death from renal failure occurred in half of them within the next eleven months. When the diet contained 40 per cent of protein, all of the rats developed chronic progressive nephritis which was usually fatal within a few months.

It is well understood that weakness and anorexia are associated with only moderate diminution in plasma volume, and that greater losses of volume cause prostration and collapse. Since normal plasma volume is dependent upon maintenance of an adequate amount of sodium in the organism, it is instructive to examine the capacity of nephritic tubule cells to do work on sodium. This can be accomplished by determining to what extent the diseased cells can reduce the loss of sodium in the urine when the intake of salt is quite small. Since the organism excretes about 200 mg. of sodium from the skin each twenty-four hours even in the absence of sweating and another 50 to 75 mg. in the feces, an intake of 300 mg. of sodium daily will necessitate a reduction of urinary sodium to some 50 mg. per twenty-four hours in order to establish sodium balance. This requires an amount of work on sodium by the tubule cells which may be beyond the capacity of diseased kidneys. Figure 4 compares this capacity in a nephritic patient with the normal response. In both cases, the record begins with the institution of a diet containing 300 mg. of sodium. Since each subject received approximately maintenance calories, change in body weight is acceptable as a rough measure of change in body water. It will be seen that the sodium content of the normal urine diminished rapidly but that nevertheless a period of five days elapsed before sodium balance was reestablished. Thereafter the urine contained 40 to 100 mg. of sodium daily. During the early days when the combined loss of

sodium was greater than the dietary supply, there was an accompanying loss of body water at a diminishing rate. About one and three-quarters liters of water were lost in this way and no subjective disturbance developed. It should be noted also that the normal kidneys were able to restrict the urinary sodium to very small amounts even though the volume of urine on the last day had been increased to four liters, a procedure that required a great increase in work.

Turning now to the nephritic patient, it is seen that the sodium content of the urine diminishes less rapidly than in the normal subject. In six days the sodium in the normal urine had dropped from 2550 to 100 mg., whereas in the nephritic urine it fell only from 2800 to 1900 mg. Even more significant is the fact that on the tenth day the patient's urine still contained 800 mg. of sodium. Accordingly, the patient never achieved or even closely approached sodium balance. This continued depletion of sodium was accompanied by a large loss of water which amounted to six liters by the tenth day when the experiment was stopped because of the gravity of the clinical disturbances caused by this depletion.

Even though the circulatory collapse in this case was caused by drastic restriction of salt, it serves to call attention to the importance of recognizing that the debility, weakness and anorexia so common in chronic nephritis may have their origin in salt depletion.

Thorn⁵ and his associates have studied two striking examples of this condition. The initial blood pressure in one of the patients was 64 mm. Hg systolic and 46 diastolic. The readings in the second case were 30 systolic and zero diastolic. All of the renal function tests indicated that the kidneys were seriously damaged in both patients. Adrenal cortical hormone was of no therapeutic value, but the administration of considerable amounts of sodium chloride resulted in dramatic improvement.

The great benefit obtained by some chronic nephritics from liberal supplies of salt might seem to indicate that it is paradoxical to prescribe low salt diet in the treatment of nephritic edema. But that is not the case for the patients who are helped by salt are the ones in whom the body content of salt and water is abnormally small, whereas the edematous patients are overburdened by an excess of salt and water.

I shall conclude this presentation by asking two questions and by making a prediction.

The Questions: Will a diet that requires the least work of the tubule cells permit more patients to recover completely from the initial attack of acute nephritis, and will it slow the progress of chronic nephritis?

The Prediction: Just as our understanding of renal physiology has been very greatly enlarged by study of the glomerulus as a filter, we will make another large step forward by measuring the work performed by the tubule cells.

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DISTURBANCES IN ELECTROLYTE METABOLISM IN MAN AND THEIR MANAGEMENT*

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DISTURBANCES in electrolyte metabolism in man may develop in almost any disease at any age. Changes in body water and electrolyte form the central feature of acidosis and alkalosis, dehydration and edema, and knowledge of this field of physiology underlies all plans for parenteral and enteral feeding. No physician can fulfill his duties without considerable knowledge of this field. However, the practical applications must vary considerably according to the disease and the reaction of the patient. I remember my father telling a story of his teacher in medicine at Rush Medical College over seventy years ago. When one of the students asked what was the treatment for scarlet fever, the doctor replied: "The treatment of scarlet fever depends on what is the matter with the patient."

Back of this statement is the wisdom that all wise physicians attain that ultimately a doctor treats patients and physiological disturbances in patients rather than diseases. One cannot outline a simple treatment for electrolyte disturbances, for treatment is based on knowledge of the manifold disturbances of body water and electrolyte that demand various slightly different procedures. One can describe the various possibilities of electrolyte disturbances in man and indicate how these are met. This type of discussion is most readily carried out for one particular disease. However, for a general audience a talk about one disease would lack interest except for selected groups. I shall, therefore, try to describe certain general features of the metabolism of water and electrolyte which are useful in planning the therapy for many diseases. The discussion must assume that the listener is willing to think about the subject and will do some additional reading and re-orientate his

* From the Department of Pediatrics, Yale University School of Medicine. Given 13 October 1947 at the Graduate Fortnight of The New York Academy of Medicine.

present views in the light of advances in our physiological knowledge, for there have been almost revolutionary changes in our concepts of electrolyte metabolism. The new knowledge has been demonstrated to have clinical application which improves our therapy strikingly.

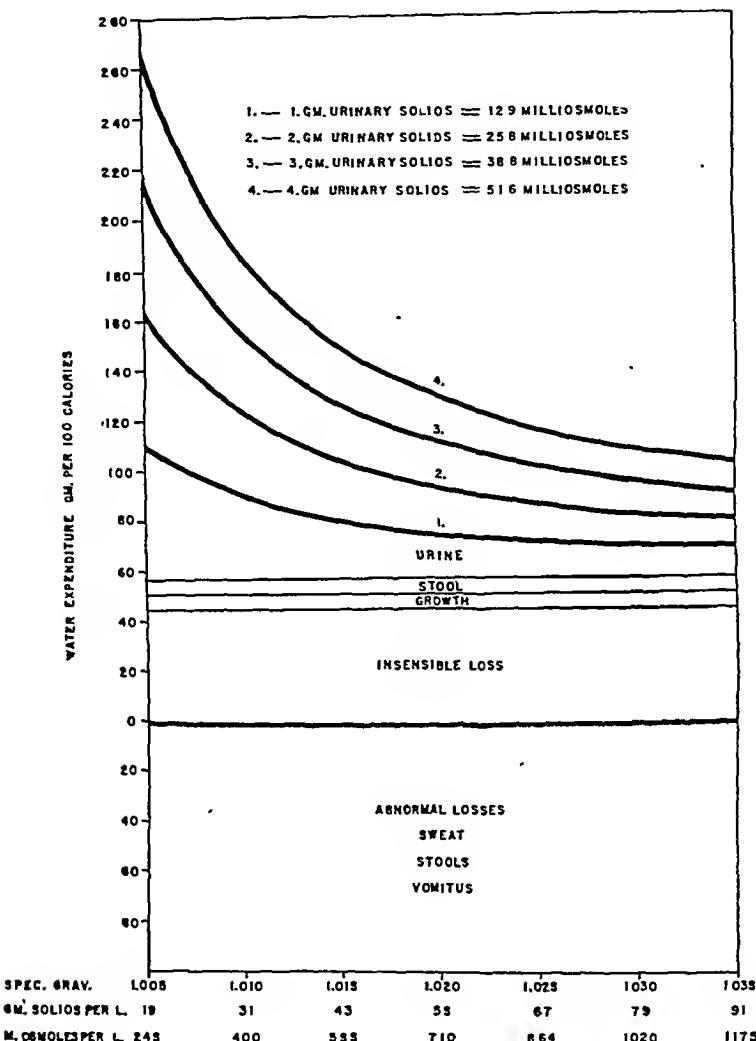
We now know some of the changes that take place in cellular electrolyte and some of the relationships between changes in extracellular and intracellular electrolyte. It is established that small amounts of sodium are normally present in cells and, under abnormal conditions, as much as half the potassium of muscle cells may be replaced by approximately equivalent amounts of sodium. Metabolic studies have demonstrated that the deficit of potassium can be replaced by administration of potassium salts and thereby strikingly improve the therapeutic results previously attained. Under certain circumstances there is a predictable relationship between serum bicarbonate and muscle composition.

In the past, pediatricians have contributed more than their share to our knowledge of fluid therapy and I believe one of the chief reasons is that, owing to the varying size of their patients, they have been forced to think in quantitative terms. My discussion will, therefore, emphasize rough quantitative data on water expenditure and the content of the body in water and electrolyte. The figures must be accepted, not as precise numbers, but as approximate averages about which patients show considerable variations.

Taking due account of the fact that water of oxidation equals about 12 per cent of the calories metabolized, the intake must equal the outgo. It has long been realized that the outgo is largely an obligatory expenditure which cannot be safely diminished by reduced intake. It is, therefore, useful in clinical practice to estimate water requirement from the physiological factors determining expenditure.

Water is excreted in the following manners: 1) By imperceptible loss from lungs and skin; 2) by sweat; 3) by stools; and 4) by urine. The imperceptible loss by lungs and skin is variable, but shows an approximate relation to caloric expenditure such that about 44 grams of water are lost from the lungs and skin for each 100 calories metabolized.¹ This water is considered practically free of electrolyte. The volume of sweat varies with the need for heat loss, but is also increased in emotional states and in vasomotor disturbances. Sweat contains sodium chloride at concentrations varying from 10 to 100 mM per liter.² The amount of sweat is usually small, except in hot weather and abnor-

CHART I—WATER EXPENDITURE PER 100 CALORIES
RELATED TO URINARY CONCENTRATION



mal states when it may be as great as several liters a day in an adult. Expressed in terms of caloric expenditure, 50 to 100 cc. per 100 calories, may be produced. Stool water is usually small (3 to 5 grams per 100 calories), but may be as great as 80 cc. in infantile diarrhea. Urine volume varies directly with the solids to be excreted and inversely with the urinary concentration.³ Since the urinary solids to be excreted are dependent on the type of intake and caloric expenditure, they may be conveniently related directly to caloric expenditure. Thus, as a first approximation, it is rational to relate total water expenditure to caloric

TABLE I
MINIMAL WATER REQUIREMENT

Urine Conc. Sp. Gravity	Baby 3 kg (300 Cal.)			Adult 70 kg (3000 Cal.)		
	Gm	Gm/kg	Gm/100 cal.	Gm	Gm/kg	Gm/100 cal.
1.005	512	171	171	4950	71	165
1.015	342	114	114	3240	46	108
1.025	282	94	94	2640	38	85

output rather than weight and thus reduce adults and babies to a common denominator. This has been done in Chart 1 and Table I. It will be noted in the chart that different lines are used for different urinary solids. If all food but glucose is omitted, the urinary solids may be close to 1 gram per 100 calories metabolized. Breast milk does not yield more solids than this. Artificially fed infants or adults usually excrete about 2 grams of solids per 100 calories. A diet high in salt or protein will increase the urinary solids and, of course, abnormal solids as in glycosuria or Addison's disease increase the urinary solids. Next it should be noted that urinary water necessary to excrete a given amount of solids decreases rapidly up to a urinary concentration measured by a specific gravity of about 1.025. But little water is saved by greater urinary concentration. If one takes into account the possibilities of urinary concentration, the chart gives one a measure of the margin of safety of a given water intake and its ability to provide extra water for sweat or abnormal losses. Infants on breast milk or many artificial feedings are given about 150 cc. per kilogram of body weight or per 100 calories. This provides about 60 cc. of water available for sweat or abnormal losses at a urinary specific gravity of 1.025 or will lead to a urinary specific gravity of 1.007, if there is no abnormal loss or sweat. The same intake of water per calorie in an adult of 70 kilograms metabolizing 3000 calories would be 4500 cc.,—permitting 1800 cc. of water for sweat or abnormal losses. It is obvious that the adult will not want this much water, except when needed and will tend to regulate his intake nearer 2500 to 3000 cc. on full caloric intake or 1500 or 2000 at bed rest and low caloric intake. However, anything which increases the caloric output, such as fever, hyperthyroidism, exercise, and so forth, will increase the water requirement. Abnormal losses or sweat must

be added to the basal requirement except when urinary concentration can provide extra water. Inability to concentrate the urine above 1.010 will increase the water required for urine formation by about 35 cc. per 100 calories or about a liter in an adult. If the urine contains abnormal amounts of salt, a provision for added urine volume must be made. It must be kept in mind that the kidneys do not concentrate, not only in chronic nephritis, but also following some surgical operations, trauma and emotional disturbances, as well as in diabetes insipidus.

Table I shows the water requirement of a baby weighing 3 kgm. and of an adult weighing 70 kilograms. In the baby, the calories metabolized are 100 per kilogram and in the adult, 43 per kilogram. It will be seen that, except for the requirement for growth, babies and adults utilize about the same amount of water per 100 calories, although their requirement per kilogram of weight differs widely. The table emphasizes the importance of metabolism rather than weight in determining water requirement.

On the other hand, if there is oliguria or anuria, the water expenditure is less by the amount of urine that is not formed. Keeping the water intake high, when urine is not excreted, will dilute body fluids, produce low electrolyte concentration and thereby aggravate the oliguria under some circumstances and even produce water intoxication. The tendency to force fluids in oliguria is almost universal, probably because deficiency of water produces oliguria and hence is relieved by replacement of body water. In such cases the deficiency usually involves electrolyte as well as water. However, when oliguria is dependent on a defect within the kidneys, maintenance of body water and electrolyte concentration at normal levels provides the best conditions for recovery of urinary function and preservation of life. This means that many types of oliguria should receive low water intakes and the body water and electrolyte concentration of such patients should be followed closely by measuring the serum electrolyte concentration frequently and keeping the body weight relatively constant.⁴ The chart shows the appropriate amounts of water to give and serum electrolyte concentration permits one to estimate the amounts of salt solution that should accompany the water; the body weight gives a rough measure of the water content of the body and permits one to estimate from day to day how successful one has been in maintaining a normal water content.

It has long been known that disturbances in body water, such as edema and dehydration, involve changes in the volume of extracellular fluids as well as changes in the concentration of extracellular electrolyte. Thus the changes in body water have come to be regarded as inter-dependent on the changes in extracellular electrolyte with which the changes in body water are associated. If there is a relative deficit of chloride in extracellular fluids, serum bicarbonate becomes high and alkalosis is demonstrable. If there is a relative deficiency of sodium, bicarbonate in serum has a low concentration and acidosis develops. To a certain extent acidosis may be explained by accumulation of abnormal acids such as aceto-acetic acid, but in general, acidosis is explained by relative or absolute deficiency of sodium. If acidosis, alkalosis, dehydration and edema involved only extracellular fluids, treatment would be possible using only the appropriate amounts of water, sodium bicarbonate and sodium chloride. However, it is now established that cellular as well as extracellular electrolytes are involved in many, if not most, disturbances in body water and electrolyte.^{5, 6} The relationships between intracellular and extracellular fluids are now beginning to be established so that it is possible to predict some of the changes in the cells and furthermore it has been proved that the changes in cellular fluid are accessible to treatment. Not only is it impossible to replace deficits of cellular electrolyte with sodium and chloride, but under many circumstances the concentrations of extracellular electrolyte remain abnormal or in an unstable state until cellular electrolyte has been restored. For example, alkalosis, in the presence of potassium deficit, may persist despite abundant available extracellular fluids and electrolyte.

The changes in intracellular electrolyte have been established almost solely for skeletal muscle, but since intracellular fluid of muscle represents about 70 per cent of the total intracellular fluid, the changes in the body as a whole can be discussed as if the changes in muscle were known to involve all cellular fluids. While muscle cells may lose some phosphorus, the chief changes involve loss of potassium, which is usually accompanied by replacement by approximately equivalent amounts of sodium. This type of change in muscle composition has been shown to develop following abnormally low intakes of potassium, such as diets low in potassium,^{7, 8} or maintenance of body fluids by parenteral administration of solutions containing only sodium, chloride and glucose.⁹ A similar picture is also produced by increased rate of

excretion of potassium following the injection of desoxycorticosterone acetate.^{10, 11} In both of these types of potassium deficit, abundant sodium chloride apparently aggravates the loss of potassium. Loss of potassium is an important feature in infantile diarrhea¹² and diabetic coma.¹³⁻¹⁶ In both of these types of potassium deficit, increased excretion in the stools or urine may account for the changes, but in addition circulatory collapse probably also plays a role. In traumatic shock due to tourniquet injury or burns, the muscles apparently lose the ability to retain potassium, and sodium enters the cells.¹⁷ Injury due to cold produces the same changes.¹⁸ Furthermore, alkalosis^{19, 20, 21} is accompanied by loss of potassium from muscle and intracellular replacement of the deficit of potassium by sodium. Recent studies²² have demonstrated a high degree of correlation between the concentration of serum bicarbonate in rats and the composition of the muscle with respect to total potassium and intracellular sodium. The condition for maintenance of this relationship is renal adjustment in the presence of a deficit of sodium or chloride or potassium. The relationship may be considered a biological adjustment or biological steady state which has considerable clinical significance.

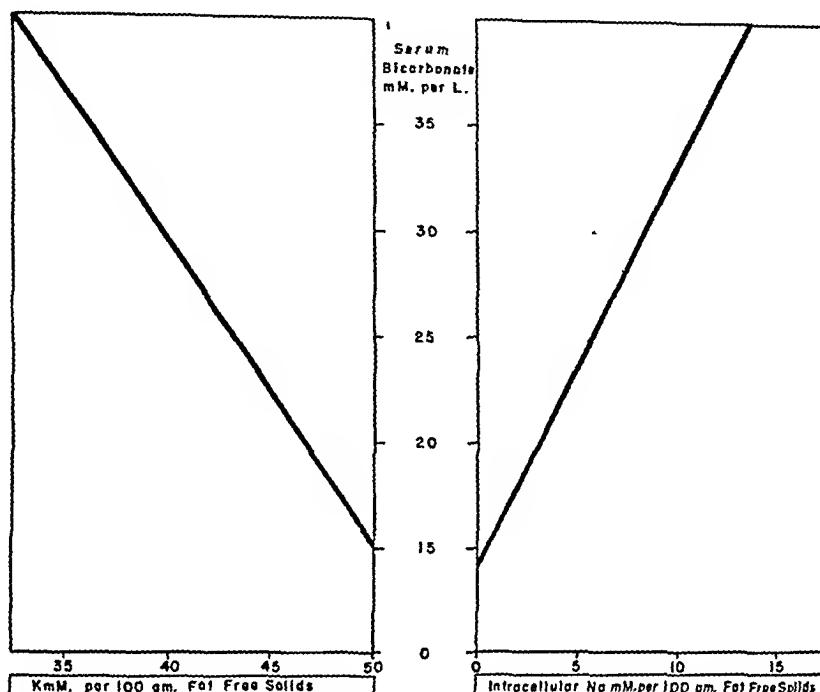
Chart 2 shows this relationship. It will be noted that serum bicarbonate concentration varies directly with intracellular sodium and inversely with muscle potassium. The relationship holds when the primary disturbance is serum alkalosis or, in other words, chloride deficiency, or when the primary disturbance is low muscle potassium or potassium deficiency and also in acidosis or sodium deficiency. In both chloride and potassium deficiency, serum bicarbonate tends to become high, while intracellular sodium is increased and muscle potassium is decreased. It follows, therefore, that chloride and potassium deficiency are similar and tend to involve a deficit of both chloride and potassium. Although extracellular sodium may be decreased, there may be little or no deficiency of sodium in the body as a whole, for the excess of intracellular sodium is likely to be equivalent to the deficit in extracellular fluids. In acidosis there is a tendency to decrease in intracellular sodium and normal or slightly high muscle potassium.

Probably the clinical significance of the quantitative relationships can best be illustrated by tables showing the estimated composition of the body as a whole.

In Table II, I have represented the composition of 10 kilograms of

CHART II

RELATION OF THE CONCENTRATION OF SERUM BICARBONATE TO MUSCLE POTASSIUM AND INTRACELLULAR SODIUM



The graphs were obtained from data on rats. The relationship will be demonstrable only when renal adjustment has been attained. The chart is useful in explaining why deficits of intracellular fluids must be considered in treating disturbances of body water and electrolyte.

TABLE II

ESTIMATED COMPOSITION OF 10 KG FAT-FREE TISSUE: NORMAL

	Concentration per Kg H ₂ O		Total Amount	
	Extracellular	Intracellular	Extracellular	Intracellular
HCO ₃ mM	25	10	70	45
Cl mM	111	3	277	13
Na mM	145	14	362	63
K mM	3	157	7	706
P mM		113		518
Solids Gm		349		1570
N Gm		53		238
H ₂ O Kgm			2.50	4.50

TABLE III
ESTIMATED COMPOSITION OF 10 KGM OF FAT-FREE TISSUE:
ALKALOSIS

	<i>Concentration per Kg H₂O</i>		<i>Total Amount</i>	
	<i>Extracellular</i>	<i>Intracellular</i>	<i>Extracellular</i>	<i>Intracellular</i>
HCO ₃ , mM	39	10	98	42
Cl, mM	105	2	263	8
Na, mM	145	37	362	156
K, mM	2	117	5	493
P, mM		113		518
Solids Gm				1570
N Gm				238
H ₂ O Kgm			2.50	4.20

* The actual weight in this case would be 9.8 kilograms owing to a deficit of intracellular water. The weight is considered 10 kilograms, because the organic structure would lead to this weight if body electrolyte were normal.

tissue of a normal baby. The proportion of extracellular fluid is 25 per cent, but 20 per cent is nearer the accepted figure for adults. The total amounts of electrolyte are obtained by multiplying the concentrations by the volumes. Total intracellular fluid is represented as having the composition of the cellular fluid of muscle and extracellular fluid is represented as having the composition of an ultrafiltrate of plasma.

The table shows high normal intracellular sodium and potassium. As was indicated in the Chart 1, intracellular sodium can be transferred to extracellular fluid in acidosis and hence can support the concentration of extracellular bicarbonate. It is, therefore, of importance that intracellular sodium is almost equivalent to the total extracellular bicarbonate or one-sixth of total extracellular sodium. On the other hand, intracellular sodium increases when serum bicarbonate is high and thus decreases the extracellular alkalosis that would result from a given change in body chloride. However, the large changes in intracellular sodium probably always involve some loss of muscle potassium.

In Table III, I have represented the state of body composition when serum bicarbonate is 35 mM per liter (81 volumes per cent). At biological adjustment this leads to a loss of about 30 per cent of muscle potassium and an increase of intracellular sodium equivalent to the

total normal extracellular sodium. Persistence of such a state depends on continued deficit of chloride or potassium.

It is obvious that potassium deficit cannot be corrected with sodium salts. It is not usually realized that severe alkalosis due to chloride deficit tends to be accompanied by potassium deficit. On the other hand, potassium deficit can lead to severe alkalosis despite abundant chloride in the diet. This fact is beautifully exemplified by those cases of Cushing's syndrome^{23, 24} which show high serum bicarbonate, low serum chloride and potassium; such cases respond to potassium salts, but fail to recover from alkalosis on sodium chloride alone. If a patient is able to take food, almost any diet contains sufficient potassium for restoration of depleted stores, but if potassium loss is increased by desoxycorticosterone acetate or the compound produced by certain adrenocortical tumors, by diarrhea, and the changes leading to diabetic coma, deficit of potassium may persist despite a normal diet. If therapy must be confined to parenteral fluids, potassium should be added to the mixtures given in order to make it possible to restore the normal composition of extracellular and intracellular fluids.

It has been demonstrated that certain types of potassium deficit do not show this relationship. Thus, in infantile diarrhea loss of potassium is apparently always a prominent feature.¹² The loss may be equivalent to as much as one-fourth of the estimated normal content of the body. Accompanying the loss of potassium, intracellular sodium may be low or high and acidosis usually accompanies the loss of extracellular electrolyte. If intracellular sodium is normal or high in the presence of acidosis, the composition of the intracellular fluid has not undergone the loss of sodium which accompanies acidosis at biological adjustment. Low muscle potassium in acidosis is also contrary to the finding of normal or high muscle potassium in acidosis. Furthermore, low or normal intracellular sodium is contrary to the finding of high intracellular sodium when potassium is lost. The absence of the relationships between serum bicarbonate and muscle composition that is found when only one ion is deficient, is presumably explained by the multiple deficiencies of the three ions in diarrhea. Whatever the explanation, the lack of the usual relationship represents an unstable state of body water and electrolyte. In diabetic coma we know that deficit of potassium as well as extracellular electrolyte is an important feature and the clinical instability of infants with diarrhea and patients with diabetic acidosis

is probably in part explained by the instability of the relationship between the concentration of extracellular fluids, and the composition of intracellular fluids. The composition of the body at biological adjustment is important in explaining the instability when the relationship is disturbed, but the particular deficits determine the final adjustment that will be attained with a given therapy.

When acidosis is treated with solutions of sodium chloride and sodium bicarbonate, it has long been recognized that the dose of sodium bicarbonate necessary to restore extracellular bicarbonate is usually greater than can be accounted for by the theoretic retention of sodium in extracellular fluids. It has been shown that this discrepancy is largely accounted for by transfer of sodium to the intracellular fluids.¹² The transfer of sodium to the cells may be dependent on the decrease in intracellular sodium which accompanies acidosis or it may be dependent on persistence of deficit of potassium which leads to excessive retention of sodium in the cells. If potassium chloride is added to fluids given parenterally, restoration of muscle potassium begins before food is taken and abnormal transfer of sodium to the cells is minimized or eliminated. On the other hand, if the administration of sodium chloride and sodium bicarbonate is continued until renal adjustment is attained in the presence of deficit of potassium, the serum bicarbonate will tend to become abnormally high. For instance, a rat with a muscle potassium of 30 mM per 100 grams of fat-free solids has about two-thirds of the normal content. At biological adjustment, this degree of potassium deficit is accompanied by a concentration of bicarbonate in serum of 40 mM per liter (95 volume per cent) and an intracellular sodium of 14 mM per 100 grams of fat-free solids. This amount of intracellular sodium is almost four times the normal value and is equivalent to three times the normal extracellular bicarbonate. Looking at the equilibrium from the point of view of the serum, profound alkalosis would be produced by the administration of sodium chloride and sodium bicarbonate until renal adjustment was reached in the presence of potassium deficit. The production of alkalosis by treating acidosis without replenishment of potassium is, therefore, not a result of failure of renal function but is the result which should be anticipated with normal renal adjustment in the presence of potassium deficit.

On the other hand, alkalosis which reaches a high degree and has persisted for some time, will lead to deficit of potassium. Administration

of sodium chloride will not overcome this alkalosis, if the potassium deficit persists. This fact explains the difficulty of overcoming some cases of alkalosis if food cannot be taken and potassium chloride is not administered.

In some babies with diarrhea, acidosis and dehydration become suddenly aggravated despite no increase in loss of water and electrolyte in the stools. This phenomenon can be explained if we assume that deficit of potassium develops slowly and intracellular sodium remains low or normal. If this unstable state leads to a rapid transfer of sodium from the extracellular to intracellular fluids, the sudden aggravation of acidosis and dehydration is readily explained. If the increase in intracellular sodium is equivalent to 5 per cent of the intracellular potassium, the decrease in extracellular sodium would be equivalent to one-half the normal extracellular bicarbonate or one-tenth of the normal extracellular sodium. Since the extracellular fluids are already depleted in a patient with diarrhea, a relatively small shift of sodium would produce a marked aggravation of extracellular dehydration and acidosis.

Deficit of potassium may be accompanied by low concentration of potassium in serum. This has been reported to be the case in gastric alkalosis,²⁵ following the administration of desoxycorticosterone acetate^{10, 11} and in the cases of Cushing's syndrome accompanied by alkalosis.^{22, 23} Infants with severe dehydration due to diarrhea or patients with diabetic coma are likely to show normal or slightly high serum potassium before treatment is begun. If infants with diarrhea^{26, 27, 28} or patients with diabetic coma^{14, 15, 16} are treated with sodium salts and glucose alone, serum potassium is likely to become abnormally low after treatment has apparently restored body water. Indeed, several diabetic patients have been described who developed paralysis analogous to familial periodic paralysis. The latter has been shown to be accompanied by low serum potassium and is relieved by administration of potassium salts.²⁵ A similar effectiveness of potassium was demonstrated in one case of diabetic coma with paralysis developing during treatment.¹⁴ Muscular paralysis has been described in dogs receiving desoxycorticosterone acetate.¹³ Thus, muscular paralysis is one of the results of potassium deficiency, but it must be regarded as relatively rare.*

* In a recent paper (Am. J. Med. Sciences, 214:153, 1947) Huang and Mao describe eleven cases of transient paralysis occurring on the second to ninth days after admission to the hospital of patients with cholera. The paralysis was regarded as analogous to that developing in familial, periodic paralysis and responded dramatically to the intravenous injection of potassium chloride. Unfortunately the authors were unable to determine the level of serum potassium. The patients had been treated with solution of sodium chloride before the paralysis developed.

Patients receiving desoxycorticosterone acetate frequently develop cardiac failure and in experimental animals myocardial necrosis develops.¹⁰ Myocardial necrosis has also been recognized in Addisonian patients dying following the administration of desoxycorticosterone acetate. Recent studies have indicated that sodium chloride in conjunction with desoxycorticosterone acetate is necessary for the production of these lesions.²⁹ However, the myocardial lesions can be produced by diets low in potassium. Cardiac enlargement and electrocardiographic changes were observed in a baby with potassium deficiency due to diarrhea.³⁰ Myocardial failure is probably one of the dangers of potassium deficit, especially in the presence of abundant sodium chloride, and should be regarded as one of the untoward results of administration of sodium chloride in the presence of potassium deficit.

As indicated above, potassium deficit is not always accompanied by low concentration of potassium in serum. In part, the author believes that high or normal serum potassium in the presence of potassium deficit is dependent on a tendency to release of potassium from the cells in dehydration, circulatory collapse and anoxia. The unmistakable establishment of the diagnosis of deficit of potassium requires a determination of the losses of body potassium or a measurement of the retention during recovery. Neither procedure is clinically practical. Paralysis, muscular weakness and atonic muscles should suggest potassium deficiency in conditions likely to develop this deficit. Enlargement of the heart or myocardial failure should also suggest potassium deficiency. However, in general, specific clinical manifestations or feasible laboratory examinations are of little help in the recognition of potassium deficiency. The author believes the diagnosis of potassium deficiency must rest largely on recognition of the conditions likely to be associated with this disturbance.

Govan and the author^{31,32} have worked out methods for treating infantile diarrhea with parenteral solutions containing sodium chloride, sodium bicarbonate and potassium chloride. The method has reduced the mortality in severe infantile diarrhea from 25-35 per cent to less than 5 per cent. The babies look better than with the old treatment, even when experience indicates that the former treatment would be successful, and there can be no doubt that potassium salts should be used in this condition and in other conditions accompanied by deficit of potassium. Similar procedures have been applied in a smaller number

TABLE IV
SOLUTION USED FOR DIARRHEA

<i>Concentration per Liter</i>			
NaCl	4.4 Gm	Na	122 mM
KCl	2.7 Gm	K	35 mM
NaHCO ₃	4.0 Gm	Cl	102 mM
		HCO ₃	55 mM

of cases of diabetic coma and in two cases of gastric alkalosis. While many details in the use of parenteral potassium remain to be worked out, sufficient is known now to indicate feasible procedures.

The chief danger in the use of potassium salts is the production of heart block. Heart block develops when the extracellular concentration rises to a little more than twice the normal value. The dose of potassium and the rate of administration must be such as not to lead to this concentration. If renal function is good, potassium is rapidly excreted when the concentration in serum rises. However, rapid intravenous administration can exceed the rate of excretion. The author has estimated that 3.5 mM of potassium or 0.26 gm. of KCl per kilogram in 24 hours is a safe dose, if used with proper precautions. The total dose should not be given in less than four hours and preferably should be given by slow drip in eight or more hours. While we originally gave potassium chloride intravenously, hypodermoclysis is now used almost exclusively for parenteral administration, since this method is safer because the rate of injection can be more reliably controlled and the fluid does not enter the blood stream directly. Administration of potassium chloride should be combined with sodium chloride or sodium chloride and sodium bicarbonate, together with intravenous glucose in water sufficient to supply the water requirement. The glucose probably facilitates the transfer of potassium to the cells.

Table IV shows the composition of the fluid used in diarrhea. This solution should be diluted with two or three parts of 5 or 10 per cent glucose in water, if given intravenously by slow drip. The solution can be given subcutaneously by slow drip without modification. Butler has advocated a similar solution already diluted for intravenous use.

His solution contains a little less sodium chloride relatively and a small amount of phosphate. I believe slightly less sodium chloride is adequate and phosphate is apparently indicated in diabetic coma, but it has not been shown to be indicated in diarrhea.

In alkalosis we are not in a position to recommend a solution from extensive direct experience. Probably a solution containing 50 mM of KCl and 50 mM of NaCl per liter will be found to be appropriate, i.e., NaCl 2.9 grams, KCl 3.7 grams per liter.

The dangers of oliguria accompanying dehydration can be avoided if some physiological salt solution and glucose solution are given before the hypodermoclyses of potassium-containing solutions are started. This will delay the administration of potassium solutions only 1 to 4 hours.

When there is no likelihood of vomiting, oral solutions are well tolerated and readily taken. The author has given orally the solution used for diarrhea, diluted with two or three parts of 5 or 10 per cent glucose in water and has offered appropriate amounts every three or four hours.

The safe dose of potassium and adequate amounts of sodium salts for marked dehydration are obtained when 80 cc. per kilogram of the solution described in Table IV are given. In any case, it must be kept in mind that the total fluid intake should be 100 to 150 cc. per 100 calories metabolized, and at least two-thirds of the water should be 5 or 10 per cent glucose in water. The glucose solution in water may be added to the salt solution, if given intravenously, but provision for administration of water without salt must always be made.

In the above discussion I have emphasized the physiological background of water and electrolyte metabolism. In practice, fluid therapy must be individualized according to the clinical disturbances, the estimated changes in body water and electrolyte, and the reaction to treatment. If fluids can be taken in adequate amounts by mouth, parenteral administration may be unnecessary. Except in renal failure, it is practically impossible to produce potassium intoxication with oral administration of potassium salts. If, owing to vomiting, diarrhea, coma or other contraindications to oral fluids, parenteral administration of fluids must be undertaken, a plan of therapy should be outlined which takes the following factors in consideration.

- 1) *Total fluid intake* should vary between 100 and 150 cc. per 100 calories metabolized, depending on the ability to form concentrated

urine and the rate of abnormal fluid loss.

2) In order to restore the deficit of water and electrolyte, 40 to 80 cc. of a solution containing salts will be necessary in dehydration. This should be added to the basic water requirement in severe cases of dehydration.

3) If there is shock, transfusion of blood and plasma or plasma should be given (10 to 30 cc. per kilogram of body weight).

4) In acidosis, the solution used to replace the electrolyte deficit should contain NaCl, NaHCO₃ and usually KCl. The mixture recommended for diarrhea has been found to lead to recovery from diarrheal acidosis without additional sodium bicarbonate or sodium lactate and the author has not seen alkalosis result from this solution. The same solution is appropriate for diabetic coma if used in conjunction with glucose and insulin; 40 to 80 cc. per kilogram meet the deficit of sodium and chloride, but the total deficit of potassium cannot be restored rapidly by parenteral fluids.

5) In alkalosis, a solution containing both sodium chloride and potassium chloride is indicated. The solution suggested above has not been tried sufficiently to establish its appropriateness by clinical observation. However, the theoretical considerations indicate that some mixture of both NaCl and KCl will prove to be more effective than physiological saline alone.

6) Before giving potassium-containing solutions by hypodermoclysis, dehydration should be treated with intravenous physiological saline and glucose (20 to 40 cc. per kilogram). This should be complemented by transfusion in all patients likely to suffer from shock.

7) If fluids cannot be taken by mouth after 12 to 24 hours, parenteral fluids should be continued so as to give 100 to 150 cc. of water per 100 calories metabolized. If loss of electrolyte continues or has not been entirely replaced, about one-fourth to one-third of the water should be given as a fluid containing an appropriate mixture of sodium chloride, sodium bicarbonate and potassium chloride.

Amino acids and plasma or plasma are indicated especially when starvation is likely to continue for several days. The sodium and chloride in each of these solutions is likely to meet the requirements for these ions. Hence, only potassium chloride and possibly phosphate is necessary to overcome the cellular deficits which are only partially replaced in the first days of treatment. About two-thirds to three-

quarters of the parenteral fluids should be given as water without salt. If the salt solution is given by hypodermoclysis, 5 to 10 per cent glucose in water should be injected slowly into a vein. If all solutions are given by vein, the glucose, amino acid and salt solutions should be mixed.

8) In patients with oliguria or anuria not dependent on water and electrolyte deficit or obstructive lesions of the genito-urinary tract, fluid therapy should be planned which will keep body water relatively constant, as indicated by the weight, and will restore and keep serum electrolyte concentrations relatively normal as indicated by serum electrolyte determinations. The fluid intake must make due allowance for the low urine volume when this is dependent on intrinsic renal failure.

9) Over short periods, the changes in body weight are the best simple guide to changes in the water content.

In summary, disturbances in water and electrolyte metabolism involve changes in the intracellular as well as extracellular fluids. In dehydration, deficits of sodium, chloride and potassium have been demonstrated and the deficit of each of these ions must be considered in treatment. The daily water administered must meet the daily expenditure. The obligate expenditure can be related to the calories metabolized and only the urinary excretion can safely save water for abnormal losses through the ability to form concentrated urine. There is a biological adjustment between the concentration of serum bicarbonate and muscle composition such that muscle potassium varies inversely with serum bicarbonate and intracellular sodium varies directly with serum bicarbonate. These relationships may be expected to be exhibited only when renal adjustment is attained in the presence of a deficit of sodium or chloride or potassium. At biological adjustment, deficits of potassium or chloride lead to similar changes in body composition. In the conditions in which the relationship of the serum bicarbonate to muscle composition is not attained, body fluids may be considered in an unstable state. The unstable state explains some of the phenomena noted in infantile diarrhea, such as the large dose of bicarbonate necessary to overcome acidosis, the sudden aggravation of acidosis and dehydration without accelerated electrolyte loss. Deficit of potassium is susceptible to parenteral and enteral therapy with improvement in the results obtained when only deficits of chloride, sodium and water were replaced.

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METABOLISM IN OLD AGE *

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IOCHEMICAL studies of the ways in which living cells utilize materials for growth, development, repair and the release of energy represent the basic level from which our knowledge of metabolism must proceed.

Studies on the enzyme systems involved in the metabolism of carbohydrates illustrate the complexity of this subject. When we seek similar information on the metabolism of other substances, such as proteins and fats, we find that our knowledge is extremely scanty and unsatisfactory. Hence, many of the important questions about the effects of aging on metabolism must await further biochemical research.

Metabolism of the total organism, however, has long been the concern of physiology, nutrition and medicine. Total oxygen consumption of the organism has come to be regarded as a useful index of the total metabolism. This index is useful because most of the chemical processes in the body require oxygen. Similarly, total balance studies, which measure the total intake and output of some specific substance, have been extensively used. However, it is important to recognize that such measurements can give only an overall picture without identifying the specific chemical processes which are involved. Nevertheless, a review of what we do know about the effects of aging on total metabolism and on the metabolism of such substances as carbohydrates, proteins, fats and minerals will be of value in charting future research needs.

CELLULAR METABOLISM

Dehydration of tissues has been traditionally regarded as a consequence of aging. Recent studies on the chemical composition of the cells in tissues from aged humans and animals, however, have failed to confirm this concept. Simms and Stolman¹ have analyzed kidney, liver, spleen and muscle tissue obtained from human material at autopsy after

* Given 14 October, 1947 at the Graduate Fortnight of The New York Academy of Medicine.

accidental or homicidal death in otherwise apparently healthy persons. Comparisons were made between a younger group of eleven individuals, ranging in age from 30 to 40 years, and an older group of six persons all over 70 years of age. On the average, sodium, water, chloride and calcium showed definite increases in the older group. In contrast, decreases were noted in potassium, magnesium, phosphorus, nitrogen and ash. These changes were in the direction to be expected if there had been an increase in extracellular fluid.

The results of Lowry and Hastings^{2,3,4} on tissue analyses of aged rats also clearly indicate a hydration rather than a desiccation of the tissues in the old animals. The water content of cells remained unchanged, whereas the water content of aged tissues increased. The authors believe that this increase in water was an extracellular edema consequent to atrophy, the loss of tissue cells, or to cardiac or renal hypofunction in the old rats. Horvath^{5,6} was unable to detect any significant decrease in water content of muscle tissue in aged rats.

Histochemical studies thus far have presented a picture of loss in the number of functioning cells and accumulation of collagen and fibrin in the tissues of aging animals but offer no evidence of functional changes in the cells which remain intact. There is no evidence of a change in the composition of the cytoplasm of cells that remain functionally active in very old individuals.

The effects of age on various cellular enzyme activities have not been systematically studied. Rosenthal, Bowie, and Waggoner⁷ have reported a decline in the respiratory oxidations of aging articular cartilage. They attribute this decline to a gradual failure of the oxygen activating component of the respiratory enzymic systems. Lazovskaya⁸ has observed a decrease in oxygen uptake in blood vessels of old rats when compared with young animals, which he believes is due to a fall in the activity of specific enzymic systems, namely, succino dehydrogenase and cytochrome oxidase systems. Glesina⁹ reported a similar reduction in the oxidation processes in muscle tissue of old animals. These studies are important in indicating possible trends; yet a great many more observations on different tissues need to be made. It is also important to find out whether the lowered oxygen consumption, if present in such aged tissues, can be stimulated by the addition of appropriate endocrine or vitamin preparations.

OXYGEN CONSUMPTION

All of the tables of normal values for basal metabolism show a progressive decline with advancing age.¹⁰⁻¹⁶ However, examination of the original data on which these norms are based, shows that very few persons above the age of 65 have been tested. Values for the higher age categories in the tables have been obtained by extrapolation of curves established on subjects of lower ages. A more extensive study of basal metabolism in aged subjects has been reported by Lewis,¹⁷ who made determinations on 45 males between the ages of 65 and 101 years. His results indicated that the individual differences in metabolic rates of older individuals were very large. In fact, many of the subjects over the age of 80 had metabolic rates as high or higher than the mean of the 40 year old group which he also studied. Despite the increased range of individual differences in the aged, statistical analysis of his observations showed a linear decrease for the average curve between the ages of 40 and 90 years. The average value for basal metabolism decreased from 36.4 calories per sq. m. per hour for the 40 to 49 year old subjects to 33.6 calories per sq. m. per hour for the 80 to 89 year old group, a total decrease of less than 10 per cent. The average basal metabolism of three subjects between the ages of 90 and 101 was 29.8 calories per sq. m. per hour. Thus, his results indicate that metabolic rate of persons over 65 is significantly lower than the value of 35 calories per sq. m. per hour shown in the tables of norms. He found no significant relationship between the apparent vigor of the individual and the metabolic rate determined in the usual manner.

The change in basal oxygen consumption with increasing age in individual subjects has been reported by Benedict.¹⁰ Measurements were made in three men who were tested repeatedly between the ages of 30-49 years, 42-59 years, and 38-57 years. Although a general decline in metabolism was observed, the irregularities in the data between observations made at short intervals are greater than the total age change observed. Studies in progress in our laboratory corroborate the finding of lowered metabolic rate in older patients as well as the increased range of individual differences.

While the gross decrease in basal metabolism cannot be denied, such determinations cannot tell us whether the oxygen utilization of individual cells in older organisms is changed or not. No method has yet

been found whereby the total amount of functioning protoplasm can be estimated in the intact human. Reduction in total metabolism may be only a reflection of the accumulation of inert non-metabolizing materials such as collagen, fat and fibrin within the body of the aged. Since histological studies all indicate a reduction in the number of functional cells in old tissue,¹⁸⁻²¹ it is quite possible that this reduction in total metabolism is simply a reflection of the reduced number of metabolizing units present in the old organism. Decreased total muscle efficiency,^{22,23} decreased muscle tone and actual muscle atrophy do occur with advancing age.²⁴ As the muscle mass contributes a major portion of the total oxygen consumption, slight reductions in the amount of this tissue would be reflected in a lower total oxygen consumption.

Because of the many physiological mechanisms available for the maintenance of homeostasis, determinations made under basal conditions may fail to show changes with age. Thus, studies of physiological responses to displacing stimuli are of great importance in assessing the degree and importance of age changes. One type of physiological stress, which is easily applied and for which many significant measurements can be made, is that of physical exercise. Only a few studies of the physiological response to exercise in aged people have as yet been made. Robinson²⁵ has, however, collected observations on physiological response in eleven adults between the ages of 60 and 80 years. Whereas the basal oxygen consumption diminished only slightly with age, the maximum oxygen consumption during exercise showed a much greater decrease in the older subjects. He also found that the increase in blood sugar level after maximal exercise was much greater in young adults than in the aged subjects. The maximum work output was also significantly lower in the old subjects, but on the average, subjects between the ages of 17 and 71 performed moderate work with about equal mechanical efficiency. However, in exhausting work there was a gradual decline in the maximum capacity for supplying energy aerobically with advancing age. Thus, there is a gradual narrowing of the margin of reserve in excess of the requirements of everyday life. It was found that the mechanisms for supplying and utilizing oxygen in exhausting work were only about 50 per cent as effective in a man of 75 as in a boy of 17. The old man was less efficient in supplying blood to active tissues, in saturating the blood with oxygen in the lungs, and in the utilization of oxygen by the tissues. Men between the ages of 30 and 40

years bring into play the lactic acid mechanism for contracting an oxygen debt to a greater extent than do the older subjects. The old men did not liberate sugar from the liver so freely as did young men when placed under severe physical stress. Thus, there are ways in which the adaptive mechanisms in the older subject showed impairment.

Observations on the cardiovascular response to exercise in a single subject from the 5th to 8th decade have been reported by Dawson and Hellebrandt.²² These observations indicated that while the maximum working capacity decreased steadily, being about 50 per cent at 71 years of what it had been at 41 years, the circulatory reaction during maximal performance was much the same at each age. Unfortunately, no metabolic or respiratory observations were included in this study. It should also be pointed out that the results can scarcely be applied to older individuals in general since the subject under observation underwent rigorous training programs and continued to be more active physically than do most people of this age. Nevertheless, there are some indications from this work that appropriate regimes of graded exercise and diet may preserve failing physiological functions in older people.

Simonson²³ has recently reviewed the literature on strength and work capacity of older men. Observations reviewed show that the age decrement in muscle strength has diminished over the past hundred years. For instance, Quetelet in 1836 found that the maximum strength of the back muscles in Belgian males was attained as a short peak at the age of 27 years, after which at the age of 30-35 years it dropped to 94 per cent of the peak strength. At 40-45 muscle strength had dropped to 89 per cent, and at the age of 50 years it was only 82 per cent of the performance at age 27. In 1921 a comparable investigation was carried out by Rejs on Dutch males. In this study the maximum strength was maintained until the age of 37 years. At the age of 40 to 45 years it was still 96 per cent of the maximum, and at the age of 50 years it had only dropped to 92 per cent. Thus, with increased life expectancy, from about 35 to 55 years over this period of time (1836-1921), there was also a better maintenance of muscle strength.

CARBOHYDRATE METABOLISM

Numerous studies have shown that when glucose is administered orally to older subjects, the maximum rise in blood sugar level is greater; and the return to normal requires longer than the usual 2½ hours.

Marshall²⁶ reported, for example, that 40 per cent of normal subjects above the age of 65 showed curves of this kind, while less than 14 per cent showed normal curves, that is, curves with a sharp rise during the first half hour from levels of 80 or 100 mg. per 100 cc. to 130 or 150 mg. per 100 cc. followed by a gradual return to normal levels within 2 to 2½ hours. John²⁷ also found only 14 per cent of normal curves in old people as compared with 82 per cent normal ones in children.

Hofstatter, Sonnenberg, and Kountz²⁸ performed oral glucose tolerance tests on 154 subjects within the age range of 50 to 86 years. On forty of these patients, who had apparently remained in about the same state of health, the oral sugar tolerance test was repeated after a period of several months to two years. Only 8.3 per cent of the patients showed normal curves, while only 5.7 per cent showed frankly diabetic types of curves. Curves showing delayed returns to normal and delayed rises accounted for over 80 per cent of the cases. Of the forty duplicate curves 50 per cent changed in type, the chief being an increase in the direction of delayed returns. The authors concluded that with progressing age over a two-year period, there is a gradual lowering of the carbohydrate tolerance but that there was no evidence of impairment of the carbohydrate metabolism in aging individuals to a degree that could be considered diabetic.

All of the studies mentioned before illustrate a diminution in carbohydrate tolerance in older people. The results, however, must be interpreted with considerable caution, since it has been shown that repeated glucose tolerance tests on the same individual may yield curves of quite different characteristics. Horvath et al.²⁹ have illustrated this variation in type of curves in the same subject. In one subject 11 consecutive oral glucose tolerance tests were carried out on successive days. Curves ranging from normal to delayed rise and delayed recovery were all observed in this subject. The authors believe that because of this variability, it is practically impossible to judge the degree of impairment of carbohydrate metabolism in aged individuals.

Since part of the variability in the oral glucose tolerance tests may be attributed to differences in rates of absorption of the administered glucose, a study of the intravenous glucose tolerance test in older people has been instituted in our laboratory at the Baltimore City Hospitals. In this study arterial blood samples drawn at ten-minute intervals following the intravenous administration of 25 grams of glucose have been

analyzed. From these data a mathematical expression for the rate of disappearance of glucose from the blood has been calculated.³⁰ Estimates of the reliability of this "elimination coefficient" lead us to believe that there are physiological changes, which alter the rate of disappearance of glucose from the circulating blood from day to day. Preliminary results indicate that in some aged males this recovery coefficient is not significantly lower than in middle-aged subjects. We have not yet tested a sufficiently large number of aged subjects to specify with certainty the average age changes. Obviously, it will be necessary to investigate the physiological factors which are important in producing these day to day variations in the recovery coefficient.

LIPID METABOLISM

Our knowledge of the effects of aging on fat and lipid metabolism is most unsatisfactory. Page and his co-workers³¹ found no significant changes in blood lipids with age. Kountz et al.³² determined blood cholesterol levels of 212 patients from 40 to 85 years of age at the St. Louis City Infirmary. An insignificant rise in cholesterol level of the men was observed between the ages of 50 and 80 with a slight drop after 80. The women showed a fairly constant level up to 70 years of age and after 70 a moderate decline. Male patients had a lower average blood cholesterol level than did the female patients of the same age. There was a general tendency in the women for elevation of blood cholesterol to accompany lowering of the basal metabolic rate, whereas among male patients this relationship did not hold. Among 21 male patients with coronary sclerosis the average blood cholesterol level was not different from that of other male patients of the same age. Thus, the authors agree with previous observations summarized by Page³³ that one must consider factors other than increased blood cholesterol level to explain the genesis of atherosclerosis in the elderly patient.

This lack of relationship between age and blood levels of lipids and cholesterol cannot be taken to mean there are no changes in lipid metabolism with age. The increased deposition of cholesterol in arterial walls,^{34,35,36} cornea of the eye, and other soft tissues^{18,37,38} well illustrates the importance of considering local changes in arteries and soft tissues which make it possible for such deposition to occur. Since atherosclerosis can develop in the absence of hypercholesterolemia, studies on tissue metabolism must be made before we can understand

the true mechanism of the development of arteriosclerosis.

Some investigators believe that a reduction in the dietary intake of lipids, particularly cholesterol, has a beneficial influence on arterial disease. While such investigations are of great importance, carefully controlled studies in which each element of the diet is evaluated have not yet been made.

Studies on lipid metabolism suffer from certain limitations. First of these is the unreliability of analytical methods for isolation and determination of specific lipid components either in blood or tissues. Secondly, tests to determine the way in which various lipid components of the diet are utilized, are still lacking. The use of various isotopes in studies of lipid metabolism has greatly advanced our knowledge within recent years. However, most of this work has been limited to animal experiments; and we still have no adequate information on individual differences among humans on the way in which fats and lipids are absorbed and utilized. Fruitful lines for future research include studies of the relationships of other substances such as choline, methionine, endocrines, etc., to the utilization of fats.

PROTEIN METABOLISM

According to studies of Benedict et al.,³⁹ Leitch and Duckworth,⁴⁰ Sherman,⁴¹ and Bricker et al.,⁴² a protein allowance of one gram per kg. of body weight per day is about 50 per cent higher than the amount of protein needed for the maintenance of nitrogen equilibrium in the normal adult on a mixed diet. Recent field studies on Army, Navy and Aviation personnel^{43, 44, 45} showed that higher protein diets improved the physical condition in young adults even though laboratory tests failed to show much improvement in actual performance. In aged subjects low protein diets have been frequently suggested because of the hazard of increased fat deposition for longevity and also as a protection against renal damage.⁴¹ The work of Newburgh and Curtis,⁴⁶ however, indicated that protein is not necessarily harmful to the normal kidney but that the degree of renal injury depends mainly on the character of the protein ingested. The proportion of protein contained in the diet and the duration of ingestion had no significant effect on the kidneys. On the other hand, kidneys previously injured by nephro-toxic substances showed greater rates of degeneration when high protein diets were ingested by the animal than when low protein diets were

fed. Although starvation has been shown by McCay^{47, 48} to increase the life span of rats, no significant change in longevity was found when the protein level of the diet was varied between 8 and 30 per cent of the total caloric intake. There is, therefore, good reason at present to question the advisability of restricting protein intake in older people provided no evidence of kidney damage is present.*

A few studies on nitrogen balance in elderly individuals have been reported on single subjects. Strieck⁴⁹ found no increased nitrogen excretion after heavy labor in a 70-year-old man, who had been living for years on a diet containing 30 grams of protein per day. Fenger⁵⁰ observed a woman over a period of 15 years, who had been maintained in nitrogen balance and a good state of nutrition on a protein intake of 1.9 to 2.2 grams per kg. of body weight per day. Kouch found five elderly men in nitrogen equilibrium, who had received 1.6 grams of protein per kg. of body weight per day. These studies do not give adequate information, first, because the number of subjects studied were too few and second, the diet offered was either not a normally balanced one or the protein intakes were 50 to 100 per cent higher than the amount recommended at present. The atrophy of body tissue in many aged individuals suggests that their protein metabolism may be disturbed.

Kountz, Hofstatter and Ackermann⁵¹ have recently reported a study on nitrogen balance in twenty-seven elderly patients. The protein intake in these patients varied from 1 to 2 grams of protein per kg. of body weight per day. Of these patients, 40.8 per cent, or eleven patients, were in negative nitrogen balance. Eight were in equilibrium, while eight others tended to retain nitrogen and were in a positive balance. A protein intake of 1.0 to 1.2 grams per kg. of body weight per day was insufficient to maintain positive nitrogen balances in five out of six elderly subjects. These findings suggest that the protein requirement of the aged is higher than usually assumed and certainly is higher than the accepted standard allowance of 1 gram per kg. of body weight per day. The authors believe that poor food habits, incomplete absorption, and metabolic changes are all factors in the negative nitrogen balances.

Although such studies of total nitrogen balance are of value in deciding upon dietary regimes for older people, additional studies on the

* Previous studies from our laboratory have indicated a reduction in kidney function in elderly subjects (Shock, N. W., *Geriatrics*, 1946, 1: 232) even in the absence of clinical signs of kidney disease. We are not yet able to say with certainty whether this reduction in kidney function indicates true kidney injury or whether it indicates only a reduction in kidney blood flow. If it can be shown that kidney damage of some degree exists in all elderly people, it may be wise to reduce, or at least select, the protein intake in the elderly.

utilization of various amino acids and other protein components are clearly needed if we are to understand the effect of aging on protein metabolism as such.

ELECTROLYTE METABOLISM

The deposition of calcium in soft tissues such as arteries, cartilage, etc., which is observed in many old persons, may be regarded as evidence of failure of the regulation of calcium metabolism in old age. Regulation of calcium metabolism includes such diverse factors as functional activity of the parathyroid glands, dietary calcium, phosphate, and vitamin D intake, the degree of physical activity, the acidity or alkalinity of the gastrointestinal tract, and others. It is little wonder, therefore, that our information about the effect of aging on calcium metabolism is so inadequate. Changes in calcium metabolism are even characteristics of aging in lower animals. Lansing^{52, 53} has found that in rotifers, planaria and toads, calcium accumulates in the cell membranes of old organisms and that removal of the deposited calcium will increase longevity at least in the rotifer. In mammals the factors involved in the deposition of calcium in arterial walls and other soft tissues are much more complex. Histological studies of the parathyroid glands do not support the hypothesis that hypo or hyperfunction of these glands plays a significant part in the impairments of the aged. Blood calcium does not change systematically with age according to recent studies by Kirk and his co-workers⁵⁴ although earlier studies⁵⁵ have reported a decrease in serum calcium with age. The reputed decrease in the power of healing or repair of bones in old patients may be more closely related to circulatory impairments than to actual impairments of calcium metabolism or decreased activity in the parathyroid glands. Here again, progress requires studies of conditions in the cells which determine the deposition of calcium.

Although the daily requirements for calcium and other minerals has been extensively studied in growing children, our knowledge of the mineral requirements for aged individuals is extremely scanty. Kane and McCay⁵⁶ have clearly shown that in aged hamsters and rats the absorption of calcium is diminished. A higher calcium intake was required in the old animals in order to prevent negative calcium balances. Owen⁵⁷ studied the calcium balance in ten aged male subjects and concluded that deficiency of calcium in the diet was the cause of negative

calcium balance in the aged. Since aging may produce changes in absorption, it is quite probable that the requirements for calcium and other minerals are greater in older people than in those of middle age.

DISCUSSION

From this brief summary of our knowledge about metabolism in old age, it is clear that there are a great many more questions in this area than there are answers. This problem must be attacked by biochemists, physiologists, and clinicians. Biochemists must further elucidate the effects of aging on cellular metabolism and exchange. It is important to know whether the enzyme systems and the pathways of utilization are the same in old tissues as in young ones. Rather than await the results of research in this area, it is important that physiologists examine the total physiological response of the organism to various food substances. Such a program will require not only estimates of the total oxygen consumption but also the ways in which specific materials are utilized by older organisms. The absorption, utilization and excretion of carbohydrates, fats, proteins, and minerals as well as the effects of vitamins and other accessory food substances on these processes must be studied in collaboration with clinicians, physiologists, and nutritionists. It is probable that aging is more the result of failures in the coördination between various physiological systems of the body than the result of impaired metabolism of individual cells. The application of physiological stress to the systems involved will be a most useful research technique since it is by such procedures that reserve capacities for performance can be evaluated. Such experiments will also provide information as to supportive techniques, such as administration of vitamins and hormones, which may be applied to alleviate whatever impairments are the results of the aging process.

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THE USE OF ANDROGENS IN MEN*

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ANDROGENS have been used therapeutically in men in well over thirty seemingly unrelated clinical situations or diseases. As with other new drugs, early exploration suggested areas of usefulness in which the claims of clinical benefit now seem unwarranted. There have also been relatively poorly explored areas where androgens now appear to be the only useful therapeutic agents.

Our decision, as to whether or not androgens should be applied in a given situation, is based upon the answer to the following questions (Testosterone and its esters are to date the most accessible and economical means of administering androgens, therefore "testosterone" is used hereafter):

- 1) Does testosterone produce any effect in condition "X"?
- 2) Is the effect beneficial or ultimately or potentially harmful in condition "X"?
- 3) Can the effect be produced more physiologically by other means in condition "X"? (i.e. is testosterone the drug of choice?).

Using the answers to the above questions as the basis for classification, it has been noted that four groups of situations exist:—

CHART I—SITUATIONS IN WHICH TESTOSTERONE HAS BEEN APPLIED

1. Where it produces a *Desirable Response* and is the drug of choice.
2. Where it produces a *Response* but is *Not* the drug of choice.
3. Where it elicits a response that is *Highly Undesirable*.
4. Where it produces no specific beneficial effect.

The clinical conditions to be discussed will be grouped according to the above classification.

* Given October 16, 1947, before the Graduate Fortnight of The New York Academy of Medicine.

I. SITUATIONS IN WHICH TESTOSTERONE PRODUCES A DESIRABLE RESPONSE AND IS THE DRUG OF CHOICE

All the clinical conditions meeting these requirements have the common denominator of being instances of *primary testicular (Leydig cell) failure*. Primary Leydig cell failure must be differentiated from Leydig cell failure secondary to failure of hypophyseal gonadotrophin secretion. In each type clinical and laboratory manifestations of androgen deficiency may be present to an equal degree. The two kinds of Leydig cell failure are difficult to separate by noting the history and physical examination only. Since each type requires different treatment and since each has a different ultimate prognosis, such separation is very necessary. Separation may be accomplished by each of three measures:

- 1) Obtaining a testicular biopsy and examining it microscopically. In primary testicular failure defects involving the testis itself are often noted. In secondary testicular failure the lack of gonadotrophin stimulation is reflected by the microscopic anatomy of the testis.
- 2) Determining the amount of urinary gonadotrophic hormones.¹ In primary testicular failure they are elevated to from 10 to 20 times that of the average for normal men. In secondary testicular failure urinary gonadotrophins are found to be absent or far below levels obtained for normal men. (It should be noted that gonadotrophins may be elevated in primary seminiferous tubule failure^{2,3} without a concomitant androgen deficiency.)
- 3) Applying the chorionic gonadotrophin therapeutic test.^{4,5} Chorionic gonadotrophins (synonyms: placental gonadotrophins, pregnancy urine extract, anterior-pituitary like hormone, prolan) are administered in 750 international units amounts intramuscularly twice daily for three weeks. If definite clinical improvement is noted, the case may be classified as secondary testicular failure (hypogonadotrophic hypogonadism). If no detectable response is elicited, the case may be classified as primary testicular failure (hypergonadotrophic hypogonadism).

These three differential diagnostic tests have their main application in classifying eunuchoids. Instances of the male climacteric are so rarely secondary to pituitary failure (unless accompanied by signs of total pituitary failure) that one need not apply any of the three tests for this specific purpose.

Having established the criteria for determining which patients suffer from primary testicular failure (hypergonadotrophic hypogonadism)^{4,5} we may restate that:-

CHART II—TESTOSTERONE PRODUCES A DESIRABLE RESPONSE
AND IS THE DRUG OF CHOICE IN:

PRIMARY TESTICULAR FAILURE

- This includes: A. Male Climacteric.
 B. Eunuchs.
 C. Functional Prepuberal Castrates.
 D. Klinefelter's Syndrome.

A. *The male climacteric* may have its onset at any time after puberty.⁶ It is not, as is the menopause in women, a physiological accompaniment of the ageing process. Very few, if any, bodily changes are noted, although in long standing cases one may find testicular atrophy, and slight involution of the secondary sex characteristics. The main symptoms are loss of sexual potency with or without loss of libido, nervousness, melancholia, crying spells, inability to concentrate, easy fatigability, weakness, paresthesias and occasionally hot flashes.

The male climacteric must be differentiated from psychogenic impotence and the anxiety tension states. This may be accomplished by finding in an instance of male climacteric 1) alterations in appearance of Leydig cells as revealed by studying a testicular biopsy, 2) finding a marked elevation in urinary gonadotrophins or 3) eliciting a positive response to the *therapeutic test using testosterone*.⁶

This test consists of administering 25 mgm. of testosterone propionate intramuscularly daily for two weeks. This should preferably be attended to by the nurse. Ideally the physician should not see the patient during the two-week injection period and for one week thereafter.

CHART III—THERAPEUTIC TEST USING TESTOSTERONE

PURPOSE: To differentiate the MALE CLIMACTERIC from PSYCHOGENIC IMPOTENCE and the ANXIETY TENSION STATES.

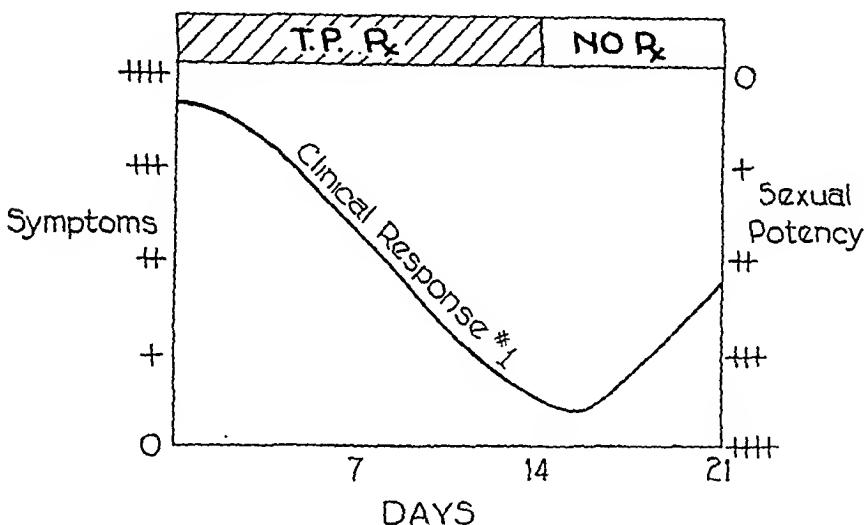
- REGIMENT: 1. Interview patient and list symptoms.
 2. Inject TESTOSTERONE PROPIONATE
 25 mgm. daily I. M. for 2 weeks.
 3. Allow 1 week to elapse (without R.)
 4. Interview patient and note change in symptomatology.

One of three responses will occur. If the patient has Leydig cell failure *gradual* alleviation of symptoms will be noticed. This will be continued for a day or two after injections are stopped. Sexual potency *gradually* returns. From the third to the seventh day after injections are stopped, symptoms and potentia tend to return toward the pretreatment level. The response is illustrated diagrammatically:—

CHART IV

THERAPEUTIC TEST USING TESTOSTERONE

Test is **POSITIVE** for MALE CLIMACTERIC if following result is obtained:



If the patient does not suffer from Leydig cell failure, either no response is elicited or, in the case of coöperative neurotics, a *sudden* change may be noted at the beginning and at the cessation of therapy. The clinical course of the latter response is not in keeping with the known physiological events effected by testosterone. The latter two courses are illustrated diagrammatically: (See Chart V.)

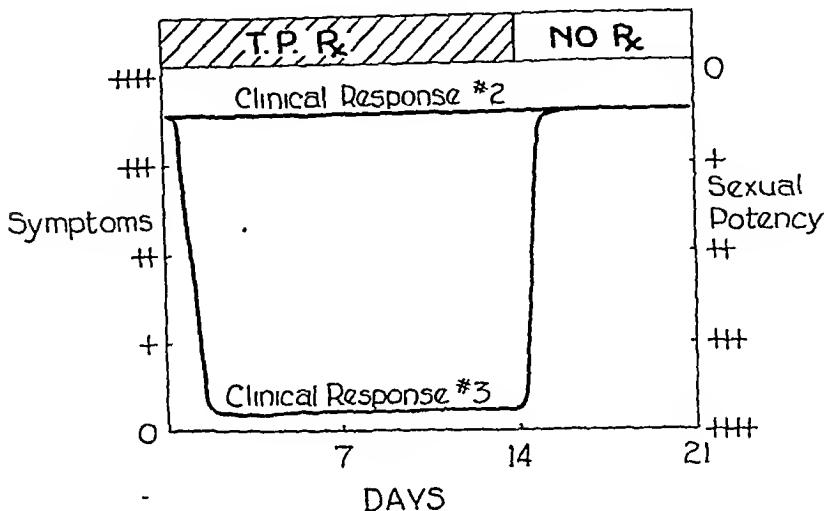
After the diagnosis of male climacteric has been firmly established by finding a) testicular damage or b) elevated urinary gonadotrophins or c) positive response to the therapeutic test using testosterone, we have treated our patients by administering testosterone propionate in oil intramuscularly or by implanting pellets of unconjugated testosterone.*

* Testosterone propionate (Oreton) and testosterone pellets (Oreton-F) have been kindly supplied us by Dr. Edward Henderson, medical director, Schering Corporation, Bloomfield, N. J.

CHART V

THERAPEUTIC TEST USING TESTOSTERONE

Test is NEGATIVE for MALE CLIMACTERIC if following result is obtained:

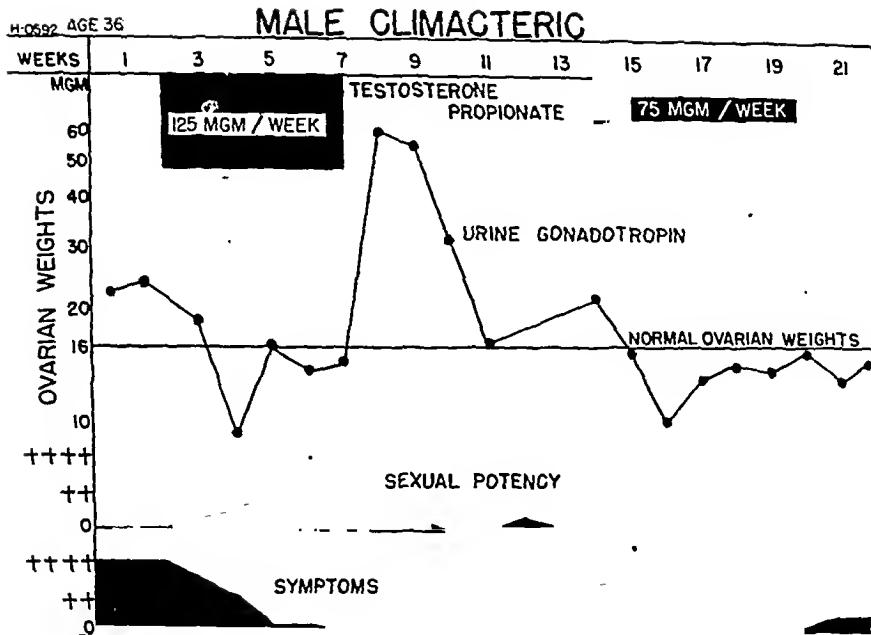


In the usual case injecting 25 mgm. of testosterone propionate three times weekly suffices. However, the amount needed varies considerably among patients and is usually determined by trial and error. The response to 25 mgm. given 4 times per week for 4 weeks, withholding treatment and the subsequent response to 25 mgm. thrice weekly is illustrated in Chart VI:-

More usually, as soon as the diagnosis is made, we implant testosterone pellets weighing 75 mgm. each. Three are placed into the subcutaneous tissue of the anterior-medial aspect of each mid-thigh. The 6 (occasionally 8) pellets exert their effects for 6 to 8 months during which time symptoms are usually minimal or absent and sexual potency is restored to normal.

B. *Eunuchs* present no problem in diagnosis and the choice of treatment is obviously replacement therapy with testosterone. Persons castrated after sexual maturation has been attained may appear not to require treatment. However, to alleviate climacteric symptoms, restore sexual vigor and produce a positive nitrogen balance in order to maintain muscle mass and strength, prevent osteoporosis, etc., therapy seems eminently worthwhile.

CHART VI



Note, although initial ovarian stimulation in the assay rats seems minimal, values of gonadotrophins obtained for normal males during this period, by the methods used, were sufficiently low so that this represents approximately a sixfold increase over normal. Note that after the first period of treatment gonadotrophins rise above pretreatment levels. This is most likely associated with temporary damage to the seminiferous tubules, caused by testosterone.

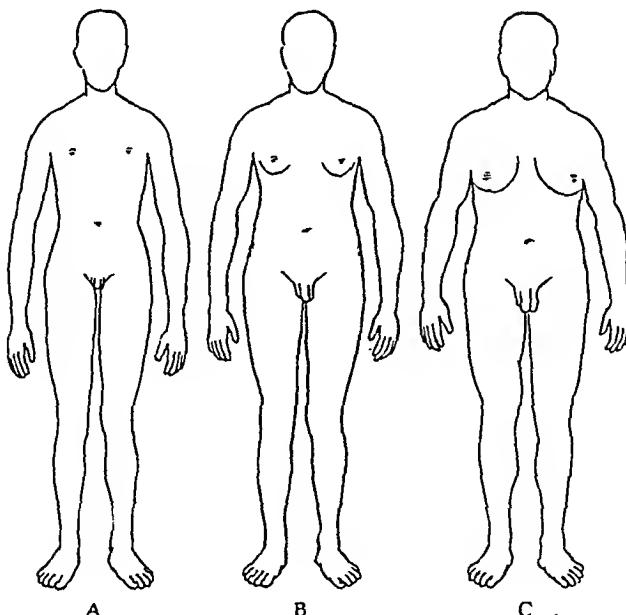


Chart VII. Schematic drawing representing the body configuration, genital and breast development of the three groups comprising the syndrome. Note the absence of gynecomastia and the under-developed genitalia in the eunuchoidal group (A); the greater development of each in the moderately eunuchoidal group (B); the association of marked gynecomastia and normal genital development in the non-eunuchoidal group (C). (Reprinted from *Journal of Clinical Endocrinology*, vol. 5, No. 1, 1945, p. 1.)

C. *Functional prepuberal castrates* are individuals who suffer from testicular agenesis or who have suffered irreparable testicular damage before the onset of puberty.⁷ Consequently they exhibit the signs and symptoms classically associated with eunuchism and sexual infantilism. Testicular biopsy often reveals that the only scrotal contents are Wolfian duct derivatives, or may reveal the remnants of the damaged testis. In either instance primary testicular atrophy may safely be assumed. Gonadotrophins are markedly elevated and the chorionic gonadotrophic therapeutic test is negative. One of the three tests must be performed prior to instituting substitutional therapy in order to rule out secondary testicular failure. Our treatment for such patients consists of either administering 25 mgm. of testosterone propionate daily or implanting eight 75 mgm. testosterone pellets. This treatment is extended until full sexual maturation is attained (usually in 2-3 years). Thereafter maintenance therapy is given. The amount is judged by trial and error.

D. *Puberal seminiferous tubule failure*. (Klinefelter's syndrome)^{8,11} is one of the most common forms of hypogonadism and unfortunately (for the patient) is least often recognized. Its main features are onset during puberty (which allows for at least some degree of sexual maturation in all cases), azoospermia, atrophic testes and elevated gonadotrophins. The main feature, invariably present, is the involvement of the seminiferous tubules. These may be completely hyalinized, contain Sertoli cells only, or, if biopsy is performed during the early stages of the condition, may contain some germinal elements. We regard the syndrome as a developmental disease having its onset just at puberty. The Leydig cells seem to be involved to some degree in all instances. The involvement at any given age may vary from almost normal (in the cases described by Klinefelter, Reifenstein and Albright⁸) to almost complete absence of function in some of our own cases.^{5,9,10} The onset at puberty coupled with the variable amount of androgen deficiency allows for a wide variation in clinical appearance, i.e. from eunuchoidal to non-eunuchoidal. (Chart VII). An example of the moderately eunuchoidal group is shown in Figures 1 and 2 in order to illustrate how very little in the way of physical signs is exhibited by the largest share of cases.

Recognition of the syndrome is important because of the great good that can be accomplished by treatment with testosterone. The patient suffering from this syndrome is psychically and physically below normal.

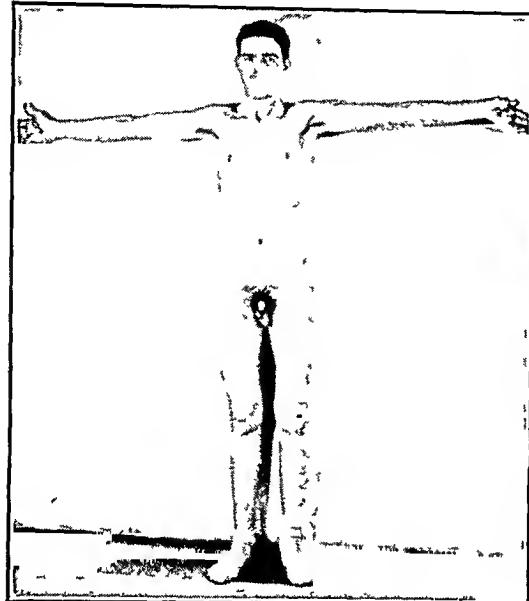


FIG. 1



FIG. 2

Puberal seminiferous tubule failure, age 22, (Case number 10 Heller & Nelson⁶), moderately eunuchoidal group. Note less than normal scrotal contents, slight gynecomastia, slightly eunuchoidal skeletal structure and lack of muscular development.

With treatment not only do the secondary sex characteristics achieve a normal level (if they were not so originally) but muscle mass, strength, endurance and vitality are all increased. With the physical changes most amazing psychic and personality changes are also achieved. The usual outcome is an improvement in the individual's usefulness to himself and to society. Treatment is the same as outlined for the functional pre-puberal castrates. Neither the gynecomastia, when present, nor the azoospermia respond in any favorable manner.

II. SITUATIONS IN WHICH TESTOSTERONE PRODUCES A RESPONSE BUT IS NOT THE DRUG OF CHOICE

In secondary testicular failure (the hypogonadotrophic syndromes) the Leydig cells fail to produce androgen because they lack pituitary stimulation. They are, however, perfectly capable of producing androgen if the proper gonadotrophin is administered. At the same time the individual will respond to androgen administration to the same extent that individuals belonging to the primary testicular failure group do. Stimulatory therapy using gonadotrophins rather than substitutional

therapy using testosterone is the treatment of choice, since in at least one of the syndromes belonging to the hypogonadotrophic group (the hypogonadotrophic eunuchoids) the patient's own pituitary will later often elaborate enough gonadotrophin to maintain the effects initiated by treatment. Administering testosterone apparently decreases the individual's chance of ever being weaned from substitutional therapy.¹² These cases of secondary testicular failure are recognized from a) the testicular biopsy, which exhibits an essentially prepuberal appearance (except in Simmonds' disease), b) lower than normal gonadotrophins and c) a positive response to the chorionic gonadotrophin therapeutic test.

CHART VIII—TESTOSTERONE PRODUCES A RESPONSE
BUT IS NOT THE DRUG OF CHOICE IN:

SECONDARY TESTICULAR FAILURE

- This includes: A. Panhypopituitary Dwarfism.
B. Panhypopituitary Cachexia (Simmonds' Disease).
C. Hypogonadotrophic Eunuchoidism.

a & b) *Panhypopituitarism* (Simmonds' disease or pituitary dwarfism) is easily recognized. The treatment of choice is stimulatory therapy using chorionic gonadotrophin as the interstitial cell stimulator.

c) *Hypogonadotrophic eunuchoidism* is differentiated from other forms of eunuchoidism by the criteria set forth above. Cases respond well to administration of chorionic gonadotrophin plus anterior pituitary extracts rich in follicle stimulating hormone. The combined treatment usually initiates spermatogenesis.^{4,5,13}

III. SITUATIONS IN WHICH TESTOSTERONES PRODUCES
A RESPONSE THAT IS HIGHLY UNDESIRABLE

The prepuberal boy will respond by early sexual maturation to the injudicious administration of testosterone at any age. This is considered to be undesirable medically (may produce eventual short stature and possibly sterility), socially (may precipitate behavioral problems) and psychologically (may result in psychic disturbances in both child and parents) and is unnecessary treatment in the first place since prepuberal boys are, by definition, lacking in androgens until the onset of puberty and so cannot be regarded as hypogonadal. Moreover, prepuberal boys

may be classed (if at all) as lacking primarily in gonadotrophins¹—thus hypogonadotropic.

CHART IX

TESTOSTERONE PRODUCES NO SPECIFIC BENEFICIAL EFFECT IN:

-
- | | |
|---------------------------|----------------------------------|
| A. Sterility. | D. Angina Pectoris. |
| B. Psychogenic Impotence. | E. Cryptorchidism. |
| C. Homosexuality. | F. Benign Prostatic Hypertrophy. |
-

IV. SITUATIONS IN WHICH TESTOSTERONE PRODUCES NO SPECIFIC BENEFICIAL EFFECT

A. *Male sterility.* Endogenous testosterone maintains the seminiferous tubules just as it maintains other elements of the male reproductive system. Thus it might be expected that exogenous testosterone would be beneficial in cases of male sterility. However, Heckel¹⁴ and McCullagh and McGurl¹⁵ demonstrated that exogenous testosterone depresses the sperm count of normal men. When therapy was stopped, sperm counts returned to pretreatment level. However, it is quite possible that permanent damage may result from such treatment as testicular biopsies obtained after cessation of treatment revealed definite histological evidence of damage to the seminiferous tubules.^{12, 14} Testosterone propionate, 25 mgm. 5 times a week will depress urinary gonadotrophin titers.^{6, 7, 11} This alone could account for the adverse effect of exogenous testosterone on spermatogenesis.

At present it would appear unwise to treat cases of male sterility with testosterone. It is theoretically possible that testosterone may prove beneficial in cases of male sterility in which the only defect is primary failure of Leydig cell secretion.

B. *Psychogenic impotence.* Impotence may be either psychogenic or hormonal in origin. It has been clearly demonstrated that testosterone will correct the impotence associated with primary Leydig cell failure of the male climacteric.⁶ It has also been claimed that testosterone is beneficial in psychogenic impotence.^{16, 17, 18} Carmichael, Noonan and Kenyon,¹⁹ however, demonstrated that cases of psychogenic impotence who responded to testosterone, responded just as well to placebo oil injections. It has also been found that psychoneurotic men could not

distinguish between testosterone and placebo oil injections whereas men with impotence due to hormonal deficiencies (male climacterics) could.⁶

Since testosterone from an exogenous source depresses spermatogenesis in men whose testicular function is normal, its use in psychogenic impotence would not only fail to correct the impotence but might render the subject sterile, at least temporarily.

The therapeutic test using testosterone will, as outlined in the section on the male climacteric, make the distinction between psychogenic impotence and the impotence due to androgen deficiency. Testicular biopsies and urinary gonadotrophin assays will do the same.

C. *Homosexuality*. There are two components to the sexual impulse direction and "drive" or intensity. Homosexuality is a disorder characterized by abnormal direction of the sexual impulse. A widely held belief is that homosexuality is due to an endocrine imbalance, i.e., that the direction of the human sexual impulse is controlled by hormones.

Evidence against such a theory is four-fold. (1) Homosexuals are indistinguishable physically from individuals with normal direction of their sex impulse.²⁰ (2) Homosexuality is no greater in hypogonadism than for the population as a whole. One of us (CGH) encountered only one instance of passive homosexuality in over 300 eunuchoids. (3) Administering estrogens in large doses is now common practice in men suffering from carcinoma of the prostate gland. To date, no report has been forthcoming (to our knowledge) that such treatment has resulted in alteration of the direction of the sex impulse. Conversely, testosterone has been administered to women for a variety of reasons. Here also there has been no report of alteration of the direction of sex interest. (4) Friedgood²¹ has administered large doses of testosterone to male homosexuals. The result has been an increase in sex drive, continuing in the same abnormal direction.

Thus, administering testosterone to male homosexuals increases the sex drive in the same abnormal direction, i.e. makes the condition worse. The situation has been summarized by Beach,^{22,23} who states, "As far as human beings are concerned . . . although the *strength* of the sexual drive may be altered by an increase or decrease in the level of gonadal hormone, the *direction* or manner of expression of sexual excitement is governed primarily by experimental factors."

D. *Angina pectoris*, a disease which by definition is subjective in

nature, which follows a fortuitous course of spontaneous exacerbations and remissions and for which no handy remedy has been discovered, is a natural target for any "new drug." Testosterone has been no exception, for it too has been repeatedly used in the treatment of angina pectoris. Only after extravagant claims had been made for several years did investigators come forward with controlled observations which clearly indicate that testosterone therapy has little if any value in the treatment of angina pectoris. (Riseman,²⁴ S. Levine and Likoff,²⁵ Hurxthal and Wilson²⁶ and E. Levine and Sellers²⁷). It has not been demonstrated that androgen deficiency accompanies angina pectoris, no specific effect of testosterone upon coronary vessels has been demonstrated, and angina pectoris has not been a consistent (and only rarely an incidental) finding in androgen deficiency. We conclude there is neither a physiological nor an empirical basis for the use of testosterone in angina pectoris.

E. *Cryptorchidism*. To an impartial observer reviewing the literature certain facts emerge concerning cryptorchidism: 1) Spontaneous descent of the testes occurs in the majority of cryptorchid preadolescent boys at the time of puberty.²⁸⁻³⁴

2) Administering testosterone, chorionic gonadotrophins or pregnant mare serum, singly or in combination, before the onset of puberty will provoke testicular descent in approximately the same percentage of cases as have spontaneous descent.³⁵⁻³⁹

3) No alterations in gross or microscopic appearance of the testis are evoked by allowing the testis to remain in an ectopic position from birth to puberty as clearly demonstrated by Rea,^{40,41} Pace,⁴² and Wangenstein.⁴³

4) After puberty marked permanent damage results to the testis if it is allowed to remain in the ectopic position (Rea^{40,41}).

For these reasons, we suggest the following program for the treatment of cryptorchidism: Do not intervene during the prepuberal period, either by use of hormones (which accelerate maturation) or by surgery (the chances of eventual successful testicular function are remote because the scrotum and spermatic cords are sufficiently undeveloped to cause the testis to remain high in the scrotum and later undergo involution). Wait for the first signs of puberty (development of the phallus, scrotum and pubic hair). If puberty appears and still no spontaneous descent occurs, it may be safely assumed that the testis is mechanically

retained. Surgery, designed to fix the testis in the scrotum, is now indicated. Any further delay may result in testicular damage. No hormonal therapy is deemed necessary in the uncomplicated case.

F. Benign Prostatic Hypertrophy. A few years ago it was fashionable to administer testosterone to patients suffering from benign prostatic hypertrophy. Improvement in symptomatology was often noted. The improvement was due to either 1) increase in bladder tonus^{44,47} or 2) the psychotherapeutic effect^{48,49,50} or 3) the normal course of the disease, which is often characterized by exacerbations and remissions.⁵¹ However, testosterone does not produce a reduction in size of the prostate.^{50,52}

The symptomatic improvement which attends the use of testosterone may be harmful in that necessary surgical measures are postponed, often to such a time as to render the operation a greater risk. Furthermore, assuming that a definite percentage of cases diagnosed as benign prostatic hypertrophy will actually have or have in addition carcinoma of the prostate, the possible harmful effects of testosterone administration become obvious.

Types of androgen therapy are tabulated below as to method of administration, chemical form, approximate dose and cost per unit effect.

CHART X
TYPES OF ANDROGEN THERAPY.

Route of Administration	Compound	Average Dosage	Relative Cost Per Unit Effect
Injection Intramuscularly	Testosterone Propionate	25 mgm. 3-5 X weekly	++
Inunction	Testosterone	5-40 mgm(?) daily	?
Oral	Methyl Testosterone	25-100 mgm. daily	++++
Sublingual	Methyl Testosterone	20-80 mgm. daily	+++
Pellet Implant Subcutaneous	Testosterone	6-75 mgm. pellets q. 6-8 months	+

As has been discussed in the body of the paper, we prefer pellet implantation to other forms of therapy. This preference is based on cost per unit effect and relative ease of administration. Effective oral therapy would be the treatment of choice if it were more economical per unit effect.

The use of testosterone to produce a positive nitrogen balance should be mentioned. In certain disorders not associated with hypogonadism a negative nitrogen balance may be converted to positive by the use of testosterone plus adequate caloric and protein intake. Discussion of this problem is not within the scope of this communication.⁵³

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SECTION ON MICROBIOLOGY

DECEMBER 17, 1947

- | | |
|---|--|
| I. EXECUTIVE SESSION
Reading of the Minutes | c. Clinical aspects
Henry G. Kunkel
Rockefeller Institute Hospital,
New York |
| II. PAPERS OF THE EVENING
INFECTIOUS HEPATITIS <ul style="list-style-type: none"> a. Etiology and epidemiology
 W. Paul Havens, Jr.
 Jefferson Medical College, Philadelphia b. Pathology
 Tracy B. Mallory
 Massachusetts General Hospital,
 Boston | |
| III. DISCUSSION
To be opened by
Perrin H. Long
Johns Hopkins University
School of Medicine, Baltimore
Gregory Shwartzman, <i>Chairman</i>
Harry Most, <i>Secretary</i> | |

The Etiology and Epidemiology of Infectious Hepatitis

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The virus of infectious hepatitis has not been "isolated" in the sense that it has been adapted to laboratory animals, although its effects have been studied in human volunteers. Thus it was shown that the virus is filtrable through a Seitz E K filter, resistant to heating to 56° C. for at least 30 minutes, and transmissible to man in serial passage by feeding or parenteral inoculation of infectious material.¹ It is present in the blood and feces of patients during the acute phase of disease,^{2, 3, 4} but the infectivity of either urine or nasopharyngeal washings has not been definitely established.⁵

Limited experiments employing a small number of volunteers have been performed to investigate the period of infectivity of patients with infectious hepatitis. Virus has been demonstrated in the blood 3 days before the appearance of symptoms,⁶ and as late as 8 days after the appearance of jaundice.⁴ A single attempt to detect virus in the blood of a patient half-way through the incubation period, as well as attempts to recover virus 1 month after onset and 3 months after disappearance of jaundice,

has been unsuccessful;³ Neefe et al.⁹ attempted to determine the infectivity of patients complaining of symptoms many months after the onset of hepatitis. Specimens of liver, obtained by biopsy, blood and feces from such patients were fed to human volunteers who developed vague symptoms and slight alterations of tests of liver function. The results were not clearly defined, and it is still not known whether such patients harbor virus or may be regarded as infectious.

EPIDEMIOLOGY

Geographic Distribution. Infectious hepatitis is widespread, and certain areas have a record of high frequency of this disease; in particular, the Mediterranean littoral has had a prolonged and high endemicity with severe epidemics among foreign troops stationed there during World Wars I and II.

Season. Although infectious hepatitis may occur at any time throughout the year, the prevalence of epidemics in the autumn and early winter months, with a decline in incidence during the spring and summer, has

been observed in many different parts of the world. The exact explanation of this seasonal trend is not known.

Age. Infectious hepatitis is primarily a disease of childhood, although it may occur at any age, as indicated by the high incidence of disease among troops in certain areas during World War II. After 30, resistance to the disease apparently increases.¹⁰

Epidemics. Both explosive and slowly developing epidemics may occur, although the latter are more usual. Family and institutional outbreaks are common. No exact reason for the frequently observed wide scatter of cases is known, although the possibility of sub-clinical cases or carriers of virus being operative in the dissemination of the disease must be considered.

The spread of hepatitis among troops has presented some interesting problems, and variations in incidence of disease in different groups have been recorded. The bulk of evidence at present suggests that variations in pathogenicity and infectivity of virus, as well as certain environmental factors such as crowding and poor sanitation in areas where the disease is highly endemic, may be important conditions in determining such differences.¹¹

Transmission of Disease. The exact way or ways in which infectious hepatitis spreads are not known, although it is not unlikely that some form of person-to-person contact is frequently operative. It is probable that more than one manner of spread are possible, and that epidemics result from different combinations of various factors.

The fact that virus is in the feces and may be transmitted experimentally by feeding such infectious materials suggests that the intestinal-oral route may be of considerable importance. Water-borne outbreaks,¹² as well as food¹³ and milk-borne¹⁴ epidemics, have been described, although there is no evidence that these are the most common modes of spread.

Transmission by the respiratory route and by insects, either by biting or by mechanical transfer of infectious materials, has been suggested, although conclusive proof is lacking. In addition, the possibility of artificial transmission of infectious hepatitis

merits consideration. The presence of hepatitis virus in the blood of patients and its high degree of infectivity by parenteral inoculation suggest the possibility that it may be transmitted accidentally more often than is recognized.

Immunity. The lack of a specific serologic test or of a susceptible laboratory animal makes it difficult to evaluate the immune response in man. The mildness of the disease in childhood suggests the possibility that infection is far more common than usually suspected, resulting in subsequent relative immunity. In support of this concept is the original observation of Stokes and Neefe,¹⁵ later corroborated by others,¹⁶ of the prophylactic value of normal adult human gamma globulin in this disease. In addition, it has been shown that human volunteers, convalescent from experimentally induced infectious hepatitis, are immune when reinoculated with an homologous strain.^{17,18}

Second attacks do occur and it is possible that immunity may not be solid; also, it is not yet determined whether such second attacks represent actual reinfection with the same virus or infection with another strain of virus.

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The Pathology of Epidemic Hepatitis

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The following paper is based upon collaborative studies with Colonel Baldwin Lucke of 296 autopsies from the files of the Army Institute of Pathology and of 160 biopsies from 137 cases of non-fatal hepatitis studied with Major T. H. Horan and Captain Leslie Jolliffe at the 15th Medical General Laboratory in Italy. Common to both fatal and non-fatal examples of the disease are inflammatory and degenerative changes in the liver. The former are essentially similar in all forms of the disease, but the latter differ markedly in the two groups of material.

The inflammatory process is evidenced by a conspicuous periportal and a relatively inconspicuous but constant intralobular infiltration of mononuclear cells. In the periportal connective tissues these consist of macrophages, lymphocytes, small numbers of eosinophiles and inconstant polymorphonuclear neutrophiles. They show no particular concentration about the biliary radicles. Within the lobule the infiltration is focal rather than diffuse and consists entirely of macrophages and swollen, occasionally proliferating Kupfer cells.

The degenerative changes in the liver cells

in fatal hepatitis are characterized by massive necrosis of a lytic type extending outward from the central vein to involve entire lobules or all but a few cells at the periphery of the lobule. This may develop with such rapidity that within two or three days of the onset of symptoms, even before clinical jaundice can develop, all liver cells in large areas will have completely disappeared. In less fulminant cases surviving ten or more days active regeneration develops from surviving cells at the periphery of the lobule producing macroscopic nodules of regeneration and the picture which has been termed multiple nodular hyperplasia.

The degenerative changes in non-fatal hepatitis are ordinarily entirely different in character. They consist of a coagulative necrosis of individual liver cells without obvious lobular orientation. The affected cells show first a deepening acidophilia and loss of granularity of the cytoplasm. They begin to shrink into a spherical shape, losing their attachments to adjacent cells and soon being extruded from the liver cord into the space of Desse. Meanwhile the nucleus becomes pyknotic, eccentric and finally disappears. Phagocytes accumulate about the hyaline sphere and eventually digest it.

The use of peritoneoscopic biopsy during an epidemic made it possible to study various stages of the disease in our volunteer patients. In cases studied during the prodromal period, active inflammatory and degenerative changes were already evident three to five days before the onset of jaundice and regeneration was already in progress as shown by numerous mitotic figures. A group of subicteric cases was recognized in which clinical jaundice never developed but daily serum bilirubin levels

showed transient rises to levels of 1.5 to 2.0 mgm. per cent. All but one of these showed typical changes, sometimes as severe as in the frankly jaundiced cases. Finally in a non-icteric group showing neither clinical nor chemical evidence of the slightest bilirubin retention characteristics changes were found in several instances. The occurrence of non-icteric hepatitis was thereby histologically confirmed.

It was also possible to study various phases of recovery and of delayed recovery. In the average case the liver had returned to a normal or nearly normal condition three or four weeks from the onset of symptoms. Focal necrosis and intralobular inflammatory foci disappeared first, periporal infiltration more slowly. In some cases of clinically normal convalescence, however, active liver cell necrosis was still present at this period, including subicteric cases which had never shown clinical jaundice.

In cases of delayed recovery in which clinical symptoms or abnormal laboratory findings persisted weeks and months after the subsidence of jaundice histologic evidence of persistent activity was also usually obvious. One case still hospitalized for persistent symptoms two and one half years after his original attack showed active inflammation and fresh focal necroses in a recent biopsy and no significant change from a specimen secured one year ago. One final group of ten cases deserves mention. Clinically diagnosed chronic hepatitis without jaundice on the basis of persistent symptoms and palpable livers but without abnormal laboratory findings and with no history of an acute attack, the biopsies uniformly failed to show changes characteristic of hepatitis.

Infectious Hepatitis: Clinical Aspects

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One of the main problems confronting clinicians interested in infectious hepatitis is why certain patients with this disease develop chronic complications while the great majority of patients recover uneventfully. The question is of particular importance at the present time because the chronic complications of the tremendous number of cases that occurred during the recent World War are gradually becoming evident.

The experience derived from a follow-up study of 400 Navy men who were admitted to the Rockefeller Hospital during 1944 and 1945 with acute infectious hepatitis has brought out some of the factors involved in the transition between acute and chronic stages of the disease.¹ At the end of two years, eight patients, or 2 per cent, showed definite evidence of impairment of liver function.

The majority of these patients demonstrated an abnormal convalescence from the acute attack which pointed toward future complications. The most common abnormality during convalescence was a relapse following the first period of full activity. This was detected by a rise in bromsulfalein retention and a delayed rise in values for the thymol turbidity test. Symptoms were usually very mild and jaundice rarely returned. Following a return to bed rest all but two of these patients recovered entirely.

The second type of abnormality during convalescence was persistent hyperbilirubinemia in the absence of other evidence of liver dysfunction. Two of these patients continued to have marked symptoms referable to the liver associated with the bilirubin elevation two years later.

The third group consisted of four patients who failed to recover from the initial attack and demonstrated marked bromsulfalein retention and symptoms of fatigue and liver tenderness for the entire two-year period. Early clinical evidence of cirrhosis appeared in this group—numerous spider

angioma, depressed serum albumin levels and occasional edema. The four patients in this group showed an average age of 32, while the average age of the 400 men was 24 years.

Sixty per cent of the total group of 400 men showed some persistent symptoms during the two-year period of follow-up, but it was almost entirely in the group who demonstrated an abnormal convalescence that liver function tests remained impaired. The remainder, although reporting such complaints as fatigue, drowsiness, intolerance to alcohol, intolerance to fatty foods, liver tenderness and diarrhea, exhibited normal liver function tests. Gradually, over the two-year period, these symptoms became less marked and most of the men recovered entirely.

All of the 400 men will have to be followed for considerably more than two years to determine the eventual outcome of the disease. The complications described in this series are probably the minimal number that occur following infectious hepatitis. The percentage and severity of complications were undoubtedly greater among the service men who developed an acute attack under wartime conditions where adequate treatment was not immediately available. A second study has been concerned with five such men who were not seen during their acute attack but were admitted to the Rockefeller Hospital at a later period of their disease and who developed a clear-cut cirrhosis of the liver.² Three of these men died and autopsy confirmed the clinical diagnosis.

Some of the factors which played a role in the development of cirrhosis in these men were apparent. First, two of the men suffered relapses under wartime conditions which were inadequately treated. Second, two of the men were over 30 years of age. Third, two of the men had severe unrelated infections after the onset of infectious hepatitis. In one case a streptococcal infection of the throat five days after the onset and,

in the other, diphtheria eight months after an uneventful recovery from acute hepatitis which brought on a severe recurrence of jaundice.

The outstanding clinical feature of the cirrhosis in these men was the malignant character of the disease once edema and ascites appeared. Nutritional forms of therapy had almost no effect on the course of the disease in distinct contrast to their value in the alcoholic type of cirrhosis. Serum albumin levels were extremely low and the injection of concentrated human serum albumin was of marked temporary benefit. However, this was purely replacement therapy and liver function did not improve. Uncontrollable bleeding from the mucous membranes was characteristic of the disease.

The futility of treatment once cirrhosis developed serves to emphasize the importance of therapeutic measures during the early stages of infectious hepatitis directed

toward the prevention of complications. Each patient should have the benefit of bedrest and a high caloric, high protein, moderate fat diet during the acute stage of the disease. During convalescence the patients should be observed with serial liver function tests for possible relapses. Patients over 30 years of age and patients with concomitant infections should be treated with special care.

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Discussion of Papers on Infectious Hepatitis

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I have been very much interested in the reports which have been made by the other speakers this evening upon the subject of Infectious Hepatitis. This disease, because of the long period of hospitalization required for its treatment, constituted one of our greatest medical problems in the North African and Mediterranean Theatres of Operations. From January 1, 1943, until June 30, 1945, more than 36,000 instances of Infectious Hepatitis were reported in troops in North Africa and Italy.

As has already been pointed out, the disease had a definite seasonal incidence beginning in both years in the late summer and reaching an epidemic peak either in November or December. In 1943, the highest incidence of the disease was noted in the 15th Air Force which at that time was moving into new bases in southeastern Italy.

The second highest incidence of infectious hepatitis in 1943 was observed in the fighting troops of the 5th Army. In 1944, the epidemic picture of this disease changed somewhat. In the base sections, the disease was not epidemic and it did not constitute much of a problem in the 15th Air Force. However, the disease was rampant in combatant troops of the 5th Army and especially in the troops of those divisions which had entered the theatre since the epidemic of 1943. I think it can be said without any question that this disease was a factor in preventing the hoped for break-through into the Po Valley in the fall of 1944.

A consideration of the factors which might be involved in the epidemic spread of this disease in North Africa and Italy certainly points to the fact that the level of sanitation in the various large troop

units could be correlated with the incidence of this disease. As units became stationary and their level of sanitation improved, the incidence of the disease decreased. This conclusion seems to be indicated by the observation that in the fall of 1945 infectious hepatitis was not epidemic in American Forces in Italy, despite the fact that most of the troops were newcomers to the Theatre. By that time sanitation was being maintained at a high level. It is believed that one of the reasons why this disease was epidemic in the forward units of the 5th Army in the fall of 1944 was the impossibility, under fighting conditions, of maintaining any real sanitary measures. One cannot escape this conclusion from a study of the natural history of infectious hepatitis in our forces in North Africa and Italy.

The aim of the Medical Corps in respect to the treatment of this disease was to get the men back to duty in condition so that they would continue on duty, in as short a time as possible. It was found that bed rest, coupled with a high protein, low fat diet

containing fresh vegetables which was acceptable to the patients, brought about the desired result. It might be stated at this point that lean beef and dried milk powder were found to be excellent and acceptable sources of protein. Another important factor in returning these patients to duty was a period of physical rehabilitation. Patients convalescent from the disease and with essentially normal liver function as determined by the bromsulfalein test, were given graded exercises over a period of ten days ending up with a day of fairly heavy exercise. If they went through this period without clinical or laboratory evidence of recurrence or relapse of the disease, then we felt quite sure that they would be able to go back to any type of duty which might be required of them. By putting our convalescent patients through this course of exercise we were able to pick up those who would have suffered a relapse after they had returned to their units. This system of therapy and rehabilitation permitted the return to full duty of over 90 per cent of the patients who had infectious hepatitis.

Abstracts of Further Discussion

Dr. Sheila Sherlock (Postgraduate Medical School of London, England) reported on aspiration liver biopsy study over the last five years of nine patients with cirrhosis developing after infective hepatitis. In the acute phase disorganization of the reticulin frame-work of the hepatic lobule is essential for consequent cirrhosis.

In three patients the liver lesion has remained well compensated. In two patients, seen soon after the acute illness, parenchymal damage was present. One of these has died of liver failure. In four patients hepatic fibrosis is prominent with associated portal hypertension. Two of these have died of gastrointestinal hemorrhage.

Infective hepatitis seems an important etiological factor in classical Laennec's cirrhosis.

Dr. S. Karelitz (Mount Sinai Hospital). In March and April of 1947 we experienced an unusual outbreak of acute fulminating hepatitis resulting in death through acute yellow atrophy of the liver in four babies and active hepatitis in two more. The first case was a 2½-year-old Puerto Rican female who had been burned on February 13. Thirty-one days later she became ill with an unexplained fever and an enlarged liver and spleen. She developed jaundice and within a few days died in cholemia.

On April 3, 1947, a 2½-month-old boy (RW) was readmitted to the hospital because of jaundice and fever of one day duration. His liver was large, the icteric index was 63, the serum alkaline phosphatase was 84 King-Armstrong units, and the urine contained bile. The child lived for

five days. Post mortem examination revealed acute yellow atrophy of the liver. He had been in the hospital because of alimentary intoxication beginning February 8, 1947, and received plasma transfusions on February 10 and on February 14 or 47 to 51 days prior to the onset of jaundice.

Another child, 2 months of age (AT) was admitted on April 3, 1947, because of jaundice and a petechial eruption over the entire body. This child died 8 hours after admission. He too had been in the hospital in February because of alimentary intoxication and received 60 cc. of plasma on February 22, February 24, and March 11, thus 37 days intervened between the first plasma transfusion and the onset of jaundice.

On April 4th (N. M.), a 6-week-old female was admitted because of a febrile illness and pallor for the previous 3 or 4 days. She had received 595 cc. of Rh negative blood during an exsanguination transfusion for erythroblastosis fetalis on February 22 at Mount Sinai Hospital. Her icteric index mounted from 12 on admission to 99. She too had bile in the urine (4 plus). Her serum alkaline phosphatase was 36 King-Armstrong units and the serum bilirubin 7.8 mgm. per cent. She died on the 8th day after admission. Her post mortem examination revealed the identical pattern of acute liver necrosis as observed in the other three patients. All four had positive cephalin flocculation reactions.

Because of the rarity of acute yellow

atrophy in this age group, the occurrence of the disease within a very short period in babies who had received plasma on the pediatric wards of Mount Sinai Hospital we felt that the source of the infection was the plasma except in the baby who had had the replacement transfusion.

All children who had been on the pediatric ward at the time these children were there were investigated and several were seen at the follow-up clinic. Of the 20 who received plasma half of them were brought back. One of these had had a febrile illness with jaundice and recovered. Another baby previously treated for alimentary toxicosis developed a very large liver and spleen and had several periods of unexplained fever since her discharge from the hospital. She recovered spontaneously. Cephalin flocculation and Thymol turbidity tests were done on the blood of the babies seen at the follow-up clinic. The results were negative in all except the two who had 2 plus cephalin flocculation reactions.

This outbreak of serum jaundice is significant because of the high mortality, the high incidence of the disease in such young babies, and the relatively short incubation period as compared to that usually observed. A detailed clinical report of these observations will be published with Drs. M. H. Bass and Ralph Moloshok and the pathological findings will be reported by Dr. P. Klemperer.

LIBRARY NOTES AND ACCESSIONS

**THE BARD COLLECTION
GIFT OF THE FRIENDS OF THE
RARE BOOK ROOM**

"The manner of my examination was as follows. on the first day I had not the most distant hint what was to be the subject o. my tryal. I went in trembling . . ." Thus wrote Samuel Bard to his father, John Bard, before recounting the questions put to him in his final examinations at Edinburgh in 1765. This correspondence between father and son provides an important source for the study of medical education in Scotland during the 1760's. These thirty-two letters with valuable biographical and genealogical material relating to Samuel Bard and his descendants constitute a unique gift made recently by the Friends of the Rare Book Room.

The Bards were the outstanding medical family of New York in their time, and it is fitting that their letters should be deposited in this Library. Those written by John Bard offer not only advice to his son but items of local interest as well. Those from Samuel's pen, besides detailing his studies, plans and adventures abroad, refer to the activities of his own countrymen. He writes with some misspelling, on December 29, 1762, "You no doubt have heard that Doctr. Shippen has opened an Anatomical Class at Philadelphia, his character here as an anatomist is very good & I dare say he shines accordingly at Philadelphia, you perhaps are not acquainted with the whole of that scheem, it is not to stop with anatomy, but to found under the Patronage of Doctr. Fothergill, a medical Colledge in that Place; Mr. Morgan who is to graduate next spring, & will be over in the fall, intends to lecture upon the Theory & Practice of Physick, and I dare say is equal to the undertaking. I wish with all my heart they were at New York, that I might have a share amongst

them, and assist in founding the first Physical Colledge in America. I do not want Ambition to prompt me to an undertaking of this kind at New York . . . but I am afraid that being so near the Phyladelphians, who will have the start of us by several years, will be a great obstacle, and another almost insurmountable one is the Parties which exist in New York; for if such a thing was to be undertaken it ought to be in conjunction with the Colledge which alone would be sufficient, to make the Presbyterian partie our enimys. . . ."

The Friends of the Rare Book Room of the Library of The New York Academy of Medicine, Inc., was organized in 1946 for the purpose of promoting interest in the possessions of the Rare Book Room and to raise funds for purchasing books, manuscripts and autograph letters to add to its collection. Besides the generous gifts already made to the Rare Book Room, the Friends have been responsible for stimulating its members to present many volumes from their own libraries. While these first efforts promise well for the future, the Friends urge all Fellows of the Academy to become members, with annual dues ranging from \$10.00 upwards. Communications should be addressed to the Secretary, Dr. Frederic D. Zeman, 17 East 89th Street.

* * *

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APRIL 1948

THE PSYCHOSOMATIC APPROACH IN
MEDICAL PRACTICE*

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THE proportionate consideration of physical and psychic factors in disease has been the medical ideal since the beginning of medicine as a discipline. In ancient Greece, Socrates, returning from army service, complained that the physicians of Hellas were less skillful than the barbarian Thracians. The latter realized that the body could not be cured without the mind, a reason that treatment of many diseases was unknown to the Greeks because they were "ignorant of the whole." Hippocrates, the Father of Medicine, also emphasized the need "to have knowledge of the whole of things" in order to bring about cure of the human body.¹ Without tracing the decline in such an idea which occurred in medicine in the intervening period we find the beginnings of our modern attempts to grasp "the whole of things" in medicine about 100 years ago. This is reviewed by Zilboorg² in a paper on the historical origins of psychosomatic medicine. He reminds us that, as late as the 18th century, psychiatry was chiefly the domain of the

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philosopher. Still in the early 19th century, preoccupation with the mental aspects of medicine was considered unscientific, a remnant of which attitude unfortunately still remains today. The accepted medical approach to mental ills was strictly in terms of the crude neuro-anatomy and pharmacology of the day. The physician interested in mental medicine, therefore, had the choice between a metaphysical approach and the crude organic one. Zilboorg also points out that the concept of the personality was slow to develop and that emotions, known as "passions," had a derogatory connotation. During this period the approach was chiefly ethical.

In 1840, however, a new attitude was crystallizing. The term "nervous disease" was introduced and was used interchangeably with "psychic" and "mental" disease, with the idea that every mental disease has a physical basis. This concept later reached a high point in 1869 with George Beard's theory of neurasthenia. In 1840, an Austrian physician used the phrase "psycho-physical totality of man." The term "personality disease" or "disturbance" was also coming into vogue. Even the term "psychosomatic," around which our discussion centers today, was anticipated in the title of a paper, "Further Discussions on the Somato-psychic Medicine," which appeared in the first volume of a new medical journal in 1838. This historical background is important to have in mind in realizing that our present emphasis on the organism as a whole is not an invention of the last 15 years but part of a recurring perspective in medicine which each time emerges with increased scientific knowledge and potency.

Our contemporary psychosomatic medicine, with its greatly added scientific armamentarium, is formed by a multitude of contributions in the last fifty years from clinical and laboratory medicine. Of special importance have been brilliant advances in endocrinology through the development of biological medicine, the physiological studies of Pavlov and Cannon, and the application of the discoveries and developments in psychoanalysis to the field of general medicine. Psychoanalysis is responsible for the establishment of the science of psychodynamics and has afforded a method of continuous and empirical study of the psyche and its bodily interrelationships, comparable in its own way to physiology and physiopathology of contemporary medicine.

There is some confusion as to the field that psychosomatic medicine embraces. In the narrower sense, it has been applied to the various

medical and surgical entities in which recent investigation has shown a large and, at times, predominantly emotional component. The better known of these are peptic ulcer, bronchial asthma, essential hypertension, Raynaud's disease, diabetes, spastic and ulcerative colitis, and a variety of dermatological conditions. The actual etiological role that personality disturbances and emotional conflict may play in these conditions awaits the further elucidation of the physiological as well as the psychological mechanisms operating. In a number of these, there is good reason to accept an important hereditary factor. This does not, however, exclude the importance of a functional trigger mechanism. Such terms as "essential hypertension" and "idiopathic ulcerative colitis" illustrate medical ignorance of the nature of the disease. Certainly any elucidation that psychological medicine can throw on the problem should be welcomed.

In the broader and, I believe, very acceptable sense, psychosomatic medicine applies to the approach enunciated at the beginning of this paper, indicating the physician's utilization, according to his training and experience, of both physical and psychological techniques in his treatment of patients. Strictly speaking, any reaction that has both psychic and physical components is psychosomatic; such are blushing, weeping, and physical expressions accompanying pleasure, anger, and anxiety. Wolf and Wolff³ have shown, through study of a subject with a permanent gastric fistula, that flushing with anger or the pallor of fear appearing in the face may be duplicated in the mucous membrane of the stomach. Many purely psychiatric conditions, such as conversion hysteria, have accompanying physical manifestations and are in this sense psychosomatic. As mentioned, so-called organic physical disease may contain a large psychological factor. In addition to what might be considered causative, every physician is acquainted with secondary emotional reactions to physical disease, whatever its origin. In this discussion, I would like to stress the broader psychosomatic approach as it applies to the practitioner or the specialist. All such persons actually practice psychosomatic medicine whether they realize it or not.

It has always been accepted that some physicians are eminently successful because of their human understanding and can utilize this understanding to promote recovery of their patients. We also recognize the fact that the general practitioner in the small community, who

knows the background, family, and acquaintances of his patient, often intuitively or consciously utilizes this knowledge in helping him to make a diagnosis or outline treatment. The ability to utilize such knowledge and understanding of the patient's personality and background has been considered as a more or less intangible asset of the individual physician and put under the heading of the art of medicine. With the recent trend towards specialization, the tendency had been to put less emphasis on these so-called "intangibles" and concentrate instead on the physical aspects of the patient's problem through technical and laboratory procedures. Now, however, the practitioner is beginning to realize the necessity of also considering personality factors in making a correct diagnosis and in planning an intelligent treatment program. Psychiatry has been the field through which such an approach has been placed on a real scientific basis.

It is not sound, however, to expect the non-psychiatrist to become a specialist in the field of psychiatry. There never can, though, be enough psychiatrists adequately to care for the neuroses which require treatment. It is therefore not only logical but imperative that the practitioner, increasingly through his medical training, be initiated into the aid which psychiatric knowledge can give him in handling his case material.

With all the popularization of psychosomatic medicine, the practitioner is generally at a loss as to how to apply the principles. Some, fired by the appeal not to neglect the emotional factor, rush in and may do more harm than good. One of the first steps, of course, is to sense that there is difficulty in the emotional sphere. The question then comes whether the practitioner himself will do something about it or will refer the case for further opinion and treatment. It is no more excusable to ride rough-shod over the sensibilities of the patient out of determination to make him confess his conflicts than it is technically excusable for an untrained and inexperienced doctor to do abdominal surgery and manhandle delicate omental tissue. One of the things that many such patients fear most is that their disclosures will not be dealt with understandingly, but will be ridiculed, laughed at, or judged harshly. An even greater fear, particularly in the hospital, is that intimate disclosures will become common property of the medical and other associated personnel. The fact that society through the law protects the inviolability of certain information given to the physician as privileged communication is an indication of the care that should be

exercised in dealing with intimate personal information. Unfortunately, the patient's fear that such disclosures may become common knowledge is too frequently realized.

It makes all the difference in the world, both in gaining and in properly using such information, whether the investigator approaches the patient as a detective who may trick him out of a confession or as an understanding and sympathetic listener who will take his cues from the patient as to how far to go and how to use these confidences to the patient's advantage. We are beginning to make progress in the training of medical students in the proper procedure in examining personality and social factors. Unfortunately, as yet there are not sufficient courses and helpful literature for those who have been out of medical school for some time. A course offered this year through the auspices of the New York County Medical Society has been an important step in the right direction. It is my purpose in this communication to lay special stress on procedure and what represents sound practice in the psychosomatic field.

Dr. Adolph Meyer, dean of psychiatry in this country and one of the early advocates for consideration of the individual as a whole, taught for many years that psychotherapeutic treatment *begins with the taking of the psychiatric history*. This also holds for the taking of the medical history insofar as the patient is suffering from emotional disturbances. To go too fast in the investigation of emotional factors or not to go far enough are equally poor procedures. The questions which are asked or are not asked indicate to the patient the sensitivity of the examiner. There is another particularly important rule for the non-psychiatric practitioner to observe, and that is not to get too deeply into the emotional material to a point which he is not qualified to handle. Only experience can give one the clue in many cases, but this understanding is as necessary for the practitioner to acquire as to know where minor surgery ends and major surgery begins.

An important part of this essential experience is developed through facility in taking a psychosomatic history, which will give the physician many clues to diagnosis which he otherwise would miss. One of the cardinal points in the approach is to allow the patient to tell his own story and not be too intent on covering only the questions in the purely medical or surgical outline of examination. Over and over the psychiatrist sees patients who have been through the hands of many

practitioners and who often have been subjected to numerous operations, without ever having had the opportunity to tell what they knew about the origin of their own disorder.

A striking example of this type of case was a woman admitted to the New York State Psychiatric Institute some years ago, who over a period of some 15 years had had 13 operations. Eventual review of the psychiatric material raised the question as to whether her whole disorder was not really a neurosis and whether most, if not all, the operations would have been unnecessary. This patient in her youth had been engaged to a physician who did not marry her. She ended by marrying a tailor whom she felt to be far beneath her aspirations, and because she could never forget her disappointment, began going to doctors with the varied complaints that arose from her dissatisfaction, unconsciously seeking the sympathy and help of a substitute for her earlier fiancé. The surgeon often succumbs to the patient's conversion symptoms, especially when reinforced by demand for operation, little realizing that the patient's neurosis uses such operative procedure for unconsciously motivated gratification. With adequate dissemination of psychiatric indications and contraindications, such operations should be considered due to gross ignorance and an evidence of inadequate diagnostic study. Although this is an extreme case, such missed diagnoses are of all too common occurrence.

The practitioner will not have time, nor will it be necessary, to take a full psychosomatic history in any but special cases. Furthermore, it is often better not to take this all at one or two sittings, but to distribute it, as will be further discussed. Any psychosomatic history, however, to be at all complete, should include a personal history, with information on early neurotic habits in childhood; schooling, including the patient's reaction to classmates and teachers; and an occupational history, which often throws important light on crises precipitating psychosomatic disease when these refer to loss of a job, financial insecurity, or personal difficulties with a fellow-employee or the employer. There should also be information on the early family background (including parents and siblings), marital status, and, if the practitioner is able to elicit it unobtrusively and skillfully, some history of the sexual development and sexual status. This latter is the portion of the history which, either through its omission or through inept handling, accounts for many missed diagnoses and much inappropriate treatment.

It is often a complaint that the psychiatrist or analyst is only interested in the sexual history. The duty of a consultant as facetiously expressed in my medical student days was to do a rectal examination, the implication being that this was what was most often neglected and gave the key to many a missed diagnosis. The psychiatrist is placed in somewhat the same position as the hypothetical consultant. Frequently, this equally important biological aspect of the situation has not been investigated, though it may give the important clue to diagnosis and treatment.

I should like to give an example from a case already reported.¹ A 28-year-old married Italian woman with diabetes, who had been for six weeks on the metabolism ward, had been complaining for a month of persistent pains and paraesthesia under the breast and over the thighs, with pulling sensations reaching to the Achilles tendons in both legs. This discomfort was especially severe when she attempted to retire for the night and would often keep her walking the floor for hours. During the day, the skin sensitiveness over the affected area forced her to reduce contact of clothing to a minimum. She had become increasingly difficult to regulate; yet no physical basis for her pain had been discovered. The psychiatrist was called for an opinion. The patient had been known to have diabetes for three years. Further history obtained by the psychiatrist threw a strong suspicion that a long and severe difference with her family over her marriage may have been important in precipitating the diabetes. The condition, however, had been regulated by diet and insulin without much medical supervision until a month or so before admission when the husband had persuaded her to consult a medical specialist. About this time, her sugar began to increase and a month later was four plus, leading to her hospitalization. After her admission, she was sugar-free for two weeks and then developed the pains and spasms described, with spilling of sugar which continued despite increased insulin and careful regulation of diet.

The hospital records showed that glycosuria was severe when the pains were at their worst and became less or disappeared when she was comparatively free from pain and spasm.

The psychiatric picture was typical of conversion hysteria. Inquiry of the patient and her husband showed that, although they had been married for two years, she was still a virgin, sexual relations having been limited to interfemoral contact. The probable relation between her

symptoms and the sexual situation was discussed with the couple, and, following discharge from the hospital, the marriage was consummated. The patient was seen in all six times over a two-month period and then lost sight of. A check made a year and a half later brought the report that she had taken the psychiatrist's advice "to have a baby," which had been her interpretation of the suggestion of better sexual hygiene. She reported that she had one child nine months old and was well along with the second. Her diabetes had been stationary but gave her no trouble. Her pains in the legs had vanished "by themselves" about a month after she stopped coming to the clinic.

Studies made at the Presbyterian Hospital^{5, 6} and elsewhere have established the fact that in many cases of diabetes it is fully as important to check on the emotional factors as on diet and exercise, and that the well-trained physician of the future will have this in mind. In many cases, the physician who becomes convinced that the patient must be cheating on the diet because of unexplained sugar will find the discrepancy in the personality area. This is particularly true in puberty and adolescence. We will not go into the question of the degree to which psychic conflict may precipitate diabetes. Experience shows, however, that frequently the time that regulation of the diabetes is undertaken is particularly opportune for some psychotherapy. The patient, from the first impact of the knowledge of his having such a serious disease, frequently reacts with a secondary depression. Some time spent in allowing him to discuss this situation with appropriate encouragement and education is indicated.

Another interesting development which is likely to occur at this initial point is that the administration of insulin, with the shocks which this frequently induces, often releases emotional discharges which may give important clues to current conflicts that may bear on later management of the disease.

One of the outstanding contributions which psychoanalysis has made to medicine is the scientific approach to an understanding of the patient-physician relationship. This was worked out originally for analytic patients because of the realization of the tremendous influence that the analyst has on the revival of early memories and the acting out of neurotic conflicts in the treatment. As a result, one of the important stages in the perfection of the psychoanalytic technique came from concentration on the understanding and management of the so-called

"transference situation."

The same principles that operate in an analysis, however, are also present to a greater or less extent in the relationship between any doctor and any patient. In fact, the same mechanism underlies, in varying degrees, the relationship between lawyer and client, teacher and pupil, pastor and parishioner, or any one of a number of professional or purely personal relationships.

Psychoanalysis has shown that the physician draws much of his intrinsic influence and authority from the fact that he reactivates in the patient attitudes which earlier obtained toward a parent, particularly the father, which tends also to reactivate the belief in magical thought which is part of the infant's and young child's orientation. The more neurotic the individual, the more exaggerated the magical power with which the physician may be invested. This phenomenon explains the success of cults and charlatanism even though the dogma propounded is without basis in adequate scientific training and experience. One of the things on which general medical practice has failed to capitalize, however, is the legitimate use of the reawakening of such archaic attitudes for the healing of body and mind.

Equipped with the experience of taking an adequate psychosomatic history, when this is indicated, and aware of the psychodynamic factors operating in the patient-physician relationship, the physician is in a position to make maximum use of his time and effort in clinical work; he is, in the sense that we have defined it, practicing psychosomatic medicine. How important it is for the therapist not to inject his own prejudices into the relationship has already been mentioned. It is necessary further to understand the reason for this in evaluating the influence which he exercises in the psychotherapeutic situation. Often the patient, after unburdening himself of some concern, may not only feel considerable mental relief, but there may be a corresponding amelioration of the psychically conditioned physical symptom. This is often multiplied over a series of contacts. The physician may be surprised because he is unaware of the dynamic situation which has been operating in treatment. If he realized, however, the role that he is playing for such a patient, he would know that often guilts that are not specifically expressed or hostilities that are not clearly enunciated are constantly being symptomatically manifested by the neurotically tense person. A sympathetic, understanding, and non-censorious attitude, which is after all

the essence of the scientific approach, can act to allay guilt about such things as early masturbation, infantile death wishes, masked guilty affection toward a parent.

It is not necessary for the physician to understand the psychodynamics operating. Many a humane and intuitive physician is constantly practicing such therapy, and his judgment in regard to human beings and their reactions in distress prevents him from the wrong sort of interference, which is in the nature of inappropriate activity and, instead of bringing relief, may aggravate the condition. That the physician should not act as a detective ferreting out hidden secrets has already been emphasized.

Particular care must be used in the attitude which the physician displays at a disclosure, not necessarily dramatic or sensational, which entails a moral issue. Earlier, in referring to the peculiar psychological position the physician holds in the unconscious mind of the patient, his authority was stressed. To whatever moral standards or experiences the physician may himself have become conditioned, he must remember that he is neither priest nor preacher and is not under obligation to strike home with some moral or religious truth which is in the domain of another profession. The patient, though the infringement confessed may be minimal or actually non-existent, is often loaded with unnecessary guilt which an unwarranted look or word may compound rather than decrease, with resultant accentuation of symptoms.

Furthermore, physicians aware of the emotional conflict may be unaware that direct advice regarding this may be useless or dangerous unless the patient himself is at the point at which he can profit by such advice, even if it does not deal with moral issues but comes rather from the physician's real grasp of the patient's needs. If not properly timed for the patient to act on it, such advice leads to further conflict. For example, the individual may be suffering from sexual frustration or need of a husband or child, but to point these out without the means of realization or the emotional stability to utilize opportunities at hand will lead to further discontent or ill-considered action, following which the last state of the patient may be worse than the first.

Even when the physician has considerable grasp of the psychodynamics operating and does not either take a moral attitude or give unwarranted advice, he still must check himself in giving injudicious interpretations of the patient's thoughts or behavior. The psychotherapy-

pist grasps the forces operating long before he is in a position to disclose these to the patient. Some of the greatest harm is done by amateur psychotherapists who, with some smattering of psychoanalytic knowledge, insist on interpreting a dream or symptomatic act directly to the patient. Not only may this lead to resentment on the part of the patient or throw him into a panic, but, if persisted in, may speed up the production of the deeper unconscious material, and the whole relationship may get badly out of hand. It is equally as important for the practitioner to realize that merely to listen continuously, thereby allowing the patient to get deeper and deeper into the material may be just as dangerous as unwarranted interpretation. In this matter of listening, it is necessary to know when to put on the brakes and what material the relatively inexperienced physician can handle with impunity. We all know that a person who is encouraged to tell a life story frequently falls in love with the listener. If the material tends to go too deeply and if the severity of the condition indicates it, the advice of the specialist, who is technically prepared to deal with such contingencies, should be sought. Unfortunately, there is no rule of the thumb that one can give; only a certain amount of experience can clarify the danger points.

The practitioner, general or specialist, can still work within the confines of his particular field and, through greater psychological insight, add to the effectiveness of his techniques, medical or surgical. In this connection, the effect of suggestion should be included in his psychodynamic understanding. The suggestibility of a patient can be an asset or liability according to how it is utilized.

First to dispose briefly of placebos. I have no quarrel with those physicians who use them skillfully. Unfortunately, they are often used with the purpose of working on the credulity of the patient with the idea afterwards of exposing him in order to drive home the functional nature of a complaint. If used purely as suggestion, the deception should be kept a secret by the physician, at least until the patient has fully recovered. In general, placebos that are pure fakes do little real good and tend to weaken good psychotherapy and undermine its right to a place in scientific medicine.

It is quite another matter, however, to obtain the maximum good from a drug or procedure by emphasizing its healing qualities. Recently an example came to my attention of the limiting of the usefulness of a medication by curtailing the patient's faith in it. An extremely tense

and jittery patient required the periodic administration of a sedative during the day. The patient had considerable faith in the effects of this drug and was able to get along with administration at fairly long intervals, until a physician explained that the effects of the medication could not possibly last more than four hours. Following this exposure of the suggestive factor in the drug, the patient would regularly have a return of his symptoms in full force at the end of the four-hour interval. Whether sedative, vitamin, or digitalis is prescribed, it is unnecessary to go into the limitations of the medication. Rather, the faith reposed in it by the patient should be intelligently reinforced, not, of course, in an insincere or exaggerated way.

Just as it is unwise to give interpretations of psychological material before the patient is ready for it, it is also poor medical practice to frighten the patient by unduly forcing other truths on him, for example, through injudicious revelation of a bad prognosis. It is true that the physician may not feel he should carry the full responsibility, with the possibility of the patient's sudden death, and that he should inform a responsible relative. However, to tell some patients with heart disease that they may have a sudden attack and die may add an anxiety state on top of a serious organic one. Even with some cardiacs who ideally might do better with restricted activity, too much restriction may, by increasing tension and restlessness, defeat the aim.

Neither should the patient be burdened with serious differences of opinion of experts, unless this is unavoidable, or discussion of other equally or more serious cases which he may inadvertently or advertently hear. A particularly damaging situation for some patients is evoked by their hearing such disagreement of opinion between specialists on a serious operation. For example, I recall the case of a nine-year-old child who overheard the opinions of two specialists, one of whom said in her presence that she would die if she were operated on and the other of whom said she would die if she were not. A later adult neurosis showed this situation to have been pivotal in a nuclear anxiety. Frequently on medical or surgical rounds, the patient overhears portions of such contradictory opinion or fragments that he does not understand, and on this builds an anxiety that may seriously interfere with management, coöperation, and convalescence. Discussion of the autopsy, for example, on the last similar case naturally gives rise to a train of disturbing thoughts to the patient who overhears it.

Under other conditions it is important for the patient to have definite information of a serious character. If the patient really wishes and needs to know the truth, the physician must use his judgment in imparting it; and under some conditions, particularly before surgical operations, it is imperative that the patient have an understanding of what awaits him. Therefore, preparation for operation should include proper psychological preparedness. The surgeon may be surprised both by the coöperativeness of the patient and the smoothness of convalescence if this preparation is done skillfully. Many children have kept lasting emotional scars from having been deceived or suddenly overpowered and anesthetized preceding a simple tonsillectomy. Adults may take an entirely different attitude toward a major operation, particularly one in which the loss of an organ or the aftermath in the way of modified function may be involved, if some clear explanation of what is to be done and what the expected results are to be is reviewed. Careful explanations preceding hysterectomy, also explaining artificial menopausal changes, are well worth the time and effort expended. It is much easier for a patient to reconcile himself to a loss that will occur than to one that has occurred.

Not only should a patient have an explanation of what is to be done, but also there should be an evaluation of the anxiety component before some procedures are instituted, because often a particular drug or procedure may be contraindicated on a particular occasion because of the amount of anxiety associated with the symptom. One of my associates at Presbyterian Hospital has made some extremely interesting observations of the importance of such a psychosomatic approach to some cases of bronchial asthma. As has been mentioned, bronchial asthma is one of the more strictly psychosomatic conditions. There is no question of the important role that allergy plays in many, perhaps the majority, of cases. We also know that the same symptom complex may be produced on a predominantly hysterical basis with all degrees in between the essentially physical and the neurotic.

In a very severe case of bronchial asthma with an undoubted neurotic component, Viola Bernard made the following observations during the patient's hospitalization when the patient was undergoing both intensive medical and psychotherapeutic treatment. The patient had three types of attacks—attacks of anxiety independent of asthma, attacks of asthma with a strong anxiety component, and attacks of asthma with

little detectable anxiety. Observation showed that certain medical treatment usually considered indicated for asthmatic attacks failed to bring results or at times even aggravated the condition, depending on the amount and distribution of the anxiety. For example, certain prodromal bronchiospasm or tachypnea which had a definite component of anxiety would usually be made worse by administration of adrenalin, while aminophyllin or a simple sedative, or both, would be more efficacious. At times even psychotherapy in the form of reassurance over the telephone was as useful as the aminophyllin or sedative. With full-blown bronchial attacks, those associated with considerable detectable anxiety would not be improved or would be worsened by adrenalin, but improved by aminophyllin or sedative, whereas in those cases with little detectable anxiety, or where, to use the technical expression, the anxiety was "bound," and the patient would outwardly be very calm before the attack, adrenalin would bring relief. In addition to a more primary anxiety that may have been the cause, overt or concealed, of an attack, there was frequently a secondary anxiety engendered by the attack itself, from the feeling of suffocation and oppression. Adrenalin did not aggravate this type, but by relieving the attack itself reduced the anxiety. It was also found that under certain circumstances, the patient failed to respond to the helium tent. Study showed that the patient had a phobia for closed places and that the panic of being in a tent often vitiated the beneficial effects of such procedure.

One of the great drawbacks for any extensive psychotherapy for the non-psychiatrist is the amount of time which it often takes and the fact that spending such time may lead the inexperienced too deeply into the neurosis. There is a great difference, however, in the efficacy of treatment if its psychological implications are recognized and appropriate means are applied in divided doses. I have already indicated that psychotherapeutic treatment starts with the taking of a proper psychosomatic history; also that the practitioner must use caution in getting too quickly and therefore too deeply into the material. Both because of time limitation and the need at times of distributing the history to prevent depth, the practitioner should learn to utilize the opportunities that he has for long, continued observation and treatment to the best psychotherapeutic advantage. The treatment of essential hypertension, where the patient may have to be followed frequently over long periods of time, often brings such an opportunity.

As the term indicates, we do not yet understand the etiology of essential hypertension. Heredity appears to play a role, but this is not a sufficient explanation since it also does in a number of other conditions about which we understand the mechanism and are able to do much to alleviate. The work of Goldblatt has stimulated new approaches to the problem; another such is the investigation of the role of the adrenal cortex in hypertension now under study at the Presbyterian Hospital in New York.⁷

Essential hypertension is considered a psychosomatic disease because of the important role personality factors appear to play in it. Carl Binger^s and collaborators have emphasized the piling up of personal tragedy in many cases which leads to a crescendo or forte and the outbreak of the disease. The individual appears frequently to be caught between his inability to roll with the punch and take life's onslaughts passively or to express his aggression and hostility and attempt to end them by a frontal attack. An insoluble life situation is often the result.

I am not advocating that the practitioner tilt at windmills in such cases. One of the most pernicious effects, however, of hypertension is the secondary anxiety and neurosis that frequently becomes engrafted on the original condition and tends to enhance it. The apprehension that frequent examination with the sphygmomanometer may engender, with endless comparison of one finding with another, may invite this. It would be much more humane and less damaging to the patient's condition to keep the blood pressure findings a matter of strict scientific record and, where possible, use other symptoms for evaluation. Whatever procedure is used, however, to measure the pressure level, the physician should try gradually to piece together the life situation. The patient should be encouraged to discuss business, family, and social worries, and thus alleviate rather than compound the anxiety. If the life situation is indeed desperate, a review by a psychiatrist familiar with these problems would be indicated. The degree to which essential hypertension may be prevented or cured by psychotherapy still awaits determination, but this should not delay the application of more superficial psychotherapy and, when possible, prevent the secondary neurosis and perhaps even stem the progress of the disease.

One of the conditions frequently seen by both practitioner and gastro-enterologist is spastic colitis. The psychiatrist sees numerous patients who have been to practitioner after practitioner, have been through

repeated gastro-intestinal series, and have been subjected to varied procedures without the physician recognizing that in the majority of such cases, he is dealing with a pure psychosomatic disease. The depression and weeping often accompanying the condition, which usually mounts with repeated examinations and unsuccessful treatments by different physicians through whose hands they pass, is usually not recognized as being the expression of the original difficulty giving rise to the physical symptoms with a secondary engrafted neurosis resulting from the futility of treatment and confusion as to what is really wrong. With a parallel personal history of work, love, or family relationships, the true nature of the condition can often be uncovered and such depression and weeping can be capitalized on for treatment, through emotional rather than physical discharge.

Naturally, such an inquiry should be made cautiously and without burdening the patient with too much insight. Recently a case came to my attention that had lasted over two years. Finally an internist grasped the situation, but could not restrain himself from passing his knowledge on directly to the patient. He told her that she was suffering from some deep unconscious conflict, that she was depressed, and that she should not read newspapers or depressing books. It was left at that, however, without pointing the way out, which, if the physician could not have done so himself, he should have called in a psychiatrist to attempt. The patient promptly became depressed, could no longer read the newspapers, particularly any accounts of accidents or suicides, and had mounting and intolerable anxiety. The depression was there—the physician had not caused it, but he had brought it to the surface precipitately. This did lead indirectly to her eventually seeking psychiatric aid, but affords an example of the wrong way to go about it.

In an earlier lecture of this series, psychosomatic aspects of colitis were referred to. The emotional component of mucous colitis has long been known. Since 1930, when Cecil Murray made a psychological investigation of ulcerative colitis, this has been added as a psychosomatic disease. At the Presbyterian Hospital and elsewhere, where ulcerative colitis has been treated psychosomatically, extremely encouraging results have come from attention to the emotional factors.^{9, 10}

Ulcerative colitis is a condition often necessitating long periods of hospitalization or confinement to home. The practitioner thus must of necessity make repeated visits. If, in addition to various, not too satis-

factory medical treatments that are in vogue, he takes occasion to review the personality and family constellation, he may find one of the cardinal conditions frequently encountered operating:

- 1) That the attack of colitis started within a few days of some situation which from that time on became a gnawing concern. This is not usually a dramatic traumatic situation, but something that the individual, due to emotional immaturity or adverse circumstances, finds it difficult to adjust to. This frequently is related to life situations like engagements, marriage, or the birth of a child.
- 2) The first situation is frequently associated with difficulty in breaking away and emancipation from a dominating figure, generally the mother, toward whom there is a great deal of unrecognized hostility.
- 3) The necessity frequently of modification of the life situation so that the patient is not continually under the domination of the mother or mother-substitute who impedes recovery. One patient characterized it succinctly: "My mother had rather have me ill at home than away and well."

We do not have time to go into details of such situations which can be found in the literature. Gradually, however, if the physician takes the trouble to inquire, the situation will often become apparent. The patient must have confidence that the physician is an ally and will not in the end betray him to the well-meaning despot from whom he seeks escape. A little extra time at the bedside or in the consulting room, distributed over the long period of medical supervision such conditions require, often will add up in the end to the equivalent of long interviews in a briefer space of time. Naturally such conferences cannot be carried out with the family or others (such as patients on the ward) present.

SUMMARY

In this paper, the attempt has been made to bring the present concept of psychosomatic medicine into historical perspective and to clarify contemporary definitions, indicating preference for the broader concept of the term as applied to all significant reactions having both a physical and emotional component. Given this base, it is clear that every physician practices psychosomatic medicine, the question only being the type of practice.

Some of the basic principles of applied psychodynamics are indi-

repeated gastro-intestinal series, and have been subjected to varied procedures without the physician recognizing that in the majority of such cases, he is dealing with a pure psychosomatic disease. The depression and weeping often accompanying the condition, which usually mounts with repeated examinations and unsuccessful treatments by different physicians through whose hands they pass, is usually not recognized as being the expression of the original difficulty giving rise to the physical symptoms with a secondary engrafted neurosis resulting from the futility of treatment and confusion as to what is really wrong. With a parallel personal history of work, love, or family relationships, the true nature of the condition can often be uncovered and such depression and weeping can be capitalized on for treatment, through emotional rather than physical discharge.

Naturally, such an inquiry should be made cautiously and without burdening the patient with too much insight. Recently a case came to my attention that had lasted over two years. Finally an internist grasped the situation, but could not restrain himself from passing his knowledge on directly to the patient. He told her that she was suffering from some deep unconscious conflict, that she was depressed, and that she should not read newspapers or depressing books. It was left at that, however, without pointing the way out, which, if the physician could not have done so himself, he should have called in a psychiatrist to attempt. The patient promptly became depressed, could no longer read the newspapers, particularly any accounts of accidents or suicides, and had mounting and intolerable anxiety. The depression was there—the physician had not caused it, but he had brought it to the surface precipitately. This did lead indirectly to her eventually seeking psychiatric aid, but affords an example of the wrong way to go about it.

In an earlier lecture of this series, psychosomatic aspects of colitis were referred to. The emotional component of mucous colitis has long been known. Since 1930, when Cecil Murray made a psychological investigation of ulcerative colitis, this has been added as a psychosomatic disease. At the Presbyterian Hospital and elsewhere, where ulcerative colitis has been treated psychosomatically, extremely encouraging results have come from attention to the emotional factors.^{9, 10}

Ulcerative colitis is a condition often necessitating long periods of hospitalization or confinement to home. The practitioner thus must of necessity make repeated visits. If, in addition to various, not too satis-

factory medical treatments that are in vogue, he takes occasion to review the personality and family constellation, he may find one of the cardinal conditions frequently encountered operating:

1) That the attack of colitis started within a few days of some situation which from that time on became a gnawing concern. This is not usually a dramatic traumatic situation, but something that the individual, due to emotional immaturity or adverse circumstances, finds it difficult to adjust to. This frequently is related to life situations like engagements, marriage, or the birth of a child.

2) The first situation is frequently associated with difficulty in breaking away and emancipation from a dominating figure, generally the mother, toward whom there is a great deal of unrecognized hostility.

3) The necessity frequently of modification of the life situation so that the patient is not continually under the domination of the mother or mother-substitute who impedes recovery. One patient characterized it succinctly: "My mother had rather have me ill at home than away and well."

We do not have time to go into details of such situations which can be found in the literature. Gradually, however, if the physician takes the trouble to inquire, the situation will often become apparent. The patient must have confidence that the physician is an ally and will not in the end betray him to the well-meaning despot from whom he seeks escape. A little extra time at the bedside or in the consulting room, distributed over the long period of medical supervision such conditions require, often will add up in the end to the equivalent of long interviews in a briefer space of time. Naturally such conferences cannot be carried out with the family or others (such as patients on the ward) present.

SUMMARY

In this paper, the attempt has been made to bring the present concept of psychosomatic medicine into historical perspective and to clarify contemporary definitions, indicating preference for the broader concept of the term as applied to all significant reactions having both a physical and emotional component. Given this base, it is clear that every physician practices psychosomatic medicine, the question only being the type of practice.

Some of the basic principles of applied psychodynamics are indi-

cated, as well as the importance of them in treatment. The place of advice, suggestion, emotional catharsis, and interpretation is discussed with these principles in mind, and with particular emphasis on what the practitioner is in a position to do psychotherapeutically.

Without attempting to make the non-psychiatrist a specialist in the field, it is imperative that the practitioner, increasingly through his medical training, be initiated into the aid which psychiatric knowledge can give him in handling his case material. This holds for the non-psychiatric specialist as well as for the general practitioner. In this way, the physician will develop a competency in the field comparable at least with the working knowledge he has of other specialties, and thus will keep abreast of the best medical practice of the day.

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ENERGY METABOLISM IN OBESE PATIENTS*

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THE statements of obese patients that they do not lose weight even though they eat scarcely anything might have been discounted. But when Von Noorden and other early students of this condition reported that some obese persons under their observation lost little or no weight while they were receiving low calory diets, it was but natural to infer that these patients were suffering from some metabolic aberration. There followed a long and arduous search for an abnormality in the energy exchange that would explain this peculiar conduct.

Basal Metabolism: It was soon reported that obese persons produce less heat per kilogram of body weight in the resting postabsorptive state than do normal controls. Had the comparison been made on the basis of height, it would have been found that the heat production of obese persons was greater than normal. But Rubner, Lusk and others had demonstrated that the basal heat production of all mammals is proportional to the area of the body surface and that no such relation exists when either weight or height alone is used as a basis of comparison.

Subsequently E. F. Du Bois¹ and his brother devised a method for calculating the area of the body surface that is suitable for clinical use and his technique has been universally accepted and employed. A few simple calculations show that with height stationary, doubling of body weight increases the area of the body surface about 40 per cent. Accordingly, in the case where basal heat production per square meter does not change as weight is gained, the heat production per kilogram will have decreased by about 40 per cent of its original value when body weight has doubled. If the obesity has developed in an adult, height will not have changed, but the basal heat production will have increased at nearly one-half the rate of the weight gain. Hence per unit of height the heat is abnormally great in obese persons. This shows the essential

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TABLE I

TOTAL BASAL HEAT PRODUCTION OF FIVE OBESE WOMEN
COMPARED WITH IDEAL VALUES

	Weight lb.	Surface Area, sq. M.	Calories/Sq. M./Hr.	Total Calories/Hr.
Ideal	129	1.59	36.5	58
Observed	238	2.06	35.5	73

fallacy of referring calories to weight as was done by the early workers in this field.

Subsequent students have without exception compared the heat produced to the surface area when they wanted to deal with metabolic rates.

Boothby and Sandiford² using modern techniques measured the heat production in 94 obese patients and found that in 81 per cent of them the rates were within the normal band. In three instances, the rates fell between minus 16 and minus 20 per cent and one patient produced heat at a rate more than 16 per cent above normal.

Strouse, Wang, and Dye³ compared the rates of normal persons with those who were underweight and overweight. They found no significant differences.

Among 180 cases of extreme obesity Grafe⁴ found only three in which there was a definite decrease in basal rate.

Since occasional persons in whom no detectable disease exists are found to have basal rates as low as minus 15 to minus 25 per cent, it is evident that obesity is not caused by a lessened expenditure of energy in the basal state.

In fact, the total heat production of obese persons is greater than it is in corresponding normal persons, because the surface area is abnormally large in the former group. Instructive data are contained in Table I, taken from the paper by Strang and Evans⁵ who compared the average values obtained from five obese women with a hypothetical normal control. It is seen that even though the heat production per square meter of body surface in the obese group is well within the normal range, nevertheless the total heat production per hour is markedly increased due to the augmented surface area.

Specific Dynamic Effect: If the heat production of a person who

has been without food for eighteen hours and who has been reclining quietly, is recorded and he is then fed, he will shortly produce more heat than he did in the fasting state. The failure to respond in this way, would result in gain of weight, provided the person continued to ingest precisely the same number of calories and provided there was no change in activity.

Several authors attempted to attribute obesity to lessened caloric response to food. However, both Dürr⁶ and Lauter⁷ emphasized the great variability in the specific dynamic response exhibited by normal persons and cast doubts upon the interpretations of earlier investigations.

Strang and McClugage,⁸ fully aware of the many hazards surrounding the measurement of the specific dynamic response to food, conducted their studies so painstakingly that they inspire great confidence. They recorded the total increase in heat production for the eight hours following the ingestion of a test meal. The average increase over the basal value in eight obese subjects was 58 calories, whereas the response of five normal persons was 51 calories. Evidently obesity is not attributable to lessened dynamic response to food.

Luxuskonsumption: Grafe⁹ conceived the idea that the heat production is influenced by the quantity of food eaten. It was postulated that the twenty-four hourly expenditure of energy increases as intake of food increases after full allowance has been made for the calories of the basal metabolism, the specific dynamic response and activity. The opposite effect would be caused by underfeeding. Obesity would result when this mechanism failed to respond to overeating. Unfortunately the experiments that Grafe performed to substantiate this hypothesis were poorly conceived and quite unconvincing. Our own studies¹⁰ give no support to Grafe's conception.

Total Metabolism: It has been repeatedly observed that obese persons who are certainly receiving only minimal quantities of food may fail to lose weight. Such paradoxical conduct could arise from some obscure metabolic abnormality that permits unusual conservation in the expenditure of energy. In that case the total heat production would be definitely less than the predicted value. Whether a disturbance of this sort does exist can be decided by recording the twenty-four hourly heat production. This may be done by indirect calorimetry with the subject enclosed in a respiration chamber. But the data will not be entirely adequate to answer the question, because the subject is neces-

TABLE II
ENERGY METABOLISM IN OBESE PATIENTS

INSENSIBLE LOSS OF WEIGHT		<i>Grams</i>
Initial body weight	70,000
Food + Water	2,800
Urine + Feces	1,600
Difference	1,200
Final body weight	70,000
Insensible loss of weight	1,200

REMOVAL OF HEAT BY EVAPORATION OF WATER

$$I.L. = \text{Water Vapor (I.W.)} + \text{CO}_2 - \text{O}_2$$

$$I.W. = I.L. - (\text{CO}_2 - \text{O}_2)$$

$$I.W. \times 0.58 = \text{Heat removed by evaporation}$$

When $I.W. = 0.93 I.L.$, then $I.L. \times 0.93 \times 0.58 = \text{Cal. lost in outgoing water vapor.}$

sarily quite inactive and the periods are limited to twenty-four or possibly forty-eight consecutive hours. Both of these limitations can be avoided by using the insensible loss of weight as a basis for the calculations. This method rests on the following considerations: Water is evaporated continuously from the skin and lungs. This is a means of removing heat since it requires 0.58 calories to convert one gram of water from the liquid to the gaseous state at usual body temperatures. This evaporation of water causes a continuous loss of weight which is slightly increased by the respiratory exchange of gases since the weight of the outgoing CO_2 exceeds that of the ingoing O_2 . This relationship is expressed by the following equation: $I.L. = I.W. + \text{CO}_2 - \text{O}_2$ where $I.L.$ is insensible loss of weight and $I.W.$ is the weight of the evaporated water. The loss of weight that occurs when the individual takes nothing by mouth and excretes no urine or feces, is the insensible loss of weight. When it is desired to measure this loss of weight for twenty-four hourly periods, it is merely necessary to add the weight of the ingestra to the initial body weight and the weight of the excreta to the final body weight and to subtract the second sum from the first one. The difference is the insensible loss of weight. These relationships are shown in Table II.

Evaporation of water takes place even when the sweat glands are completely inactive. This is the condition when violent exercise is

avoided and when the air is cool enough to permit complete comfort. Under these circumstances the weight of the water vapor varies from about 700 to 1500 grams per twenty-four hours in adults, depending upon size and activity. This corresponds to the removal of 406 calories ($700 \times .58$) to 870 calories ($1500 \times .58$) by this route.

Earlier students¹¹ had shown that there is a quantitative relationship between the hourly insensible loss and the basal metabolism. In order to determine whether the heat removed by vaporization of water is proportional to heat production for twenty-four hourly intervals on the part of persons who are leading their usual lives, the following procedures were carried out.¹² A number of individuals were placed on diets which were considered to be close to maintenance and an accurate body weight was obtained each morning at the same time under the same conditions. If there was progressive gain or loss of weight, the calories of the diet were adjusted appropriately until constancy of weight was achieved. It could then be assumed that the subjects were in energy balance and that the total loss of heat was equal to the calories of the diet. Since the composition of the diet was known, it was possible to calculate the weights of the CO_2 produced and of the O_2 absorbed. Subtraction of the difference between these two weights from the twenty-four hourly insensible loss of weight, gave the weight of the water vapor. This value was then converted to its heat equivalent by multiplying by 0.58, which is the amount of heat in calories required to change one gram of water from the liquid to the gaseous phase. From these data, the per cent of the total heat, removed by evaporation of water, was calculated. Table III shows the data obtained from twelve individuals. It will be seen that the total variation in heat removed by evaporation of water was only from 23.8 per cent to 25.2 per cent, even though the heat production varied from 2,200 to 3,600 calories per 24 hours. These studies indicate that human beings exhibit a striking tendency to rid themselves of a fixed per cent of the heat produced in twenty-four hours by vaporization of water, provided only that they are comfortable in regard to environment. Therefore total heat production can be calculated from the weight of the water vaporized. But this latter value can not be obtained directly from persons who are moving about freely. However, a few calculations show that the water vapor makes up from 93 per cent to 98 per cent of the insensible loss of weight depending upon whether relatively much or little carbohy-

TABLE III

PERCENTAGE OF TOTAL HEAT LOST BY EVAPORATION OF WATER

<i>Age yr.</i>	<i>Heat lost by Evaporation of water, Percent</i>	<i>Comment</i>
56	23.8	Diabetic Patient
30	24.2	Diabetic Patient
28	24.2	Chemist
24	24.4	Chemist
25	24.1	Medical Student
23	24.7	Graduate Student
24	25.2	Graduate Student
24	24.2	Student
18	24.3	Patient in bed
15	24.8	Patient in bed
18	24.8	Patient in bed
47	24.7	Patient in bed

TABLE IV

ENERGY METABOLISM IN OBESE PATIENTS

$$\text{Heat Production} = \text{Insensible Loss} \times 0.93 \times 0.58 \times 4.08 \\ 0.93 \times 0.58 \times 4.08 = 2.20$$

Example of Calculation of Heat Production for 24 Hours
from Insensible Loss of Weight

	<i>Gms.</i>		<i>Gms.</i>
First Body Wt.	158,450	Second Body Wt.	158,700
Food and Drink	2,920	Urine . . .	1,200
	<hr/>	Stool . . .	250
	161,370		<hr/>
			160,150

$$\text{Insensible Loss} = 161,370 - 160,150 = 1,220. 1,220 \times 2.20 = 2,684 \text{ Calories}$$

drate is being metabolized. Accordingly the insensible loss of weight, a value easily obtained, can be used conveniently as the basis for calculating the heat production.

The following equation is applicable when maintenance diets of the usual mixed variety are fed: Heat = I.L. \times 0.93 \times 0.58 \times 4.08. Simplified: Heat = I.L. \times 2.2. Where 0.93 is the per cent of the insensible loss of weight that consists of water vapor; 0.58 is the factor for converting weight of water evaporated to heat (calories); 4.08 is the factor for deriving total heat from heat lost by vaporization. An example of the calculation is seen in Table IV.

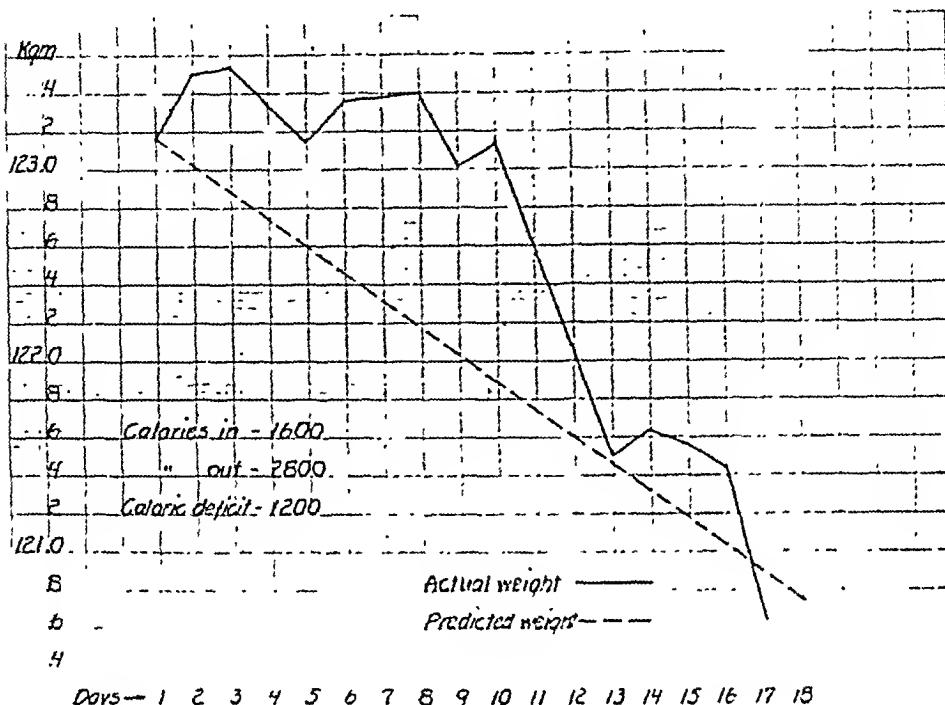


Fig. 1.

About 150 grams of body tissue were consumed daily to yield the 1200 calories not contained in the diet. Nevertheless, the body weight had declined only 100 grams by the tenth day. During the next three days, the patient lost about 1600 grams even though no change in diet had been made. The weight had now fallen to the value obtained by subtracting the weight of the body tissue destroyed during the thirteen days from the initial body weight.

In undernutrition, the same calculation is used except that the water vapor is now assumed to occupy 98 per cent of the insensible loss of weight since most of the heat is derived from the oxidation of fat. This difference is satisfied by multiplying I.L. by 2.3 instead of 2.2.

By means of this technique, the heat production of a number of obese persons was recorded consecutively in twenty-four hourly periods for several weeks and sometimes even for months. Included in the series were the various types of obesity described in the literature, namely: (1) a physically normal person except for the excessive weight, who frankly admitted years of gluttony, (2) a feeble-minded girl with a low basal rate, (3) a girl with disease of the pituitary body and a basal metabolic rate 30 per cent below normal, (4) a middle-aged woman whose weight had reached 295 pounds after an operation on the pitui-

TABLE V—ENERGY METABOLISM IN OBESE PATIENTS

FACTORS IN WATER BALANCE	
Sources of Water	Excretory Water
1. Water of food	1. Water of urine
2. Water drunk	2. Water of stool
3. Water of oxidation	3. Insensible water
4. Preformed water	

tary body eight years earlier, (5) a young woman suffering from so-called Dercum's disease, (6) a middle aged woman five feet two inches tall, whose weight had reached 420 pounds—menopausal obesity. In no instance was the heat production less than the predicted value for comparable persons of normal weight. In fact, just the opposite was true. The obese patients invariably produced more heat per twenty-four hours than similar normal persons leading comparable lives.

Nevertheless, we, as had our predecessors, encountered obese patients who while receiving low calory diets, lost no weight for a number of days. An example of this phenomenon is found in Figure 1. The patient, a young woman, weighed 275 when she entered the hospital. Her basal metabolic rate per square meter of body surface was normal; but the total basal heat production was 2100 calories per twenty-four hours, about 600 calories greater than the predicted value for a comparable woman of normal weight. She remained in bed throughout the study. However, in spite of the inactivity, her twenty-four hourly heat production averaged 2800 calories. This was at least 800 calories greater than normal. Her diet contained 1600 calories daily. This produced a deficit of 1200 calories per day and calculation from the metabolic data indicated that she was oxidizing about 150 grams of body tissue daily as a source of these 1200 calories. Nevertheless, she lost only 100 grams during the first ten days. For the next three days, without any change in treatment, she lost about 1600 grams, and this was sufficient to bring her weight down to the predicted amount for that day. This very rapid loss of weight was far in excess of what could be explained by destruction of body tissue and compensated entirely for the stationary weight during the first ten days. Such a biphasic response suggested that the patient's body water was increasing progressively during the first phase in amounts whose weight roughly equalled that of the body

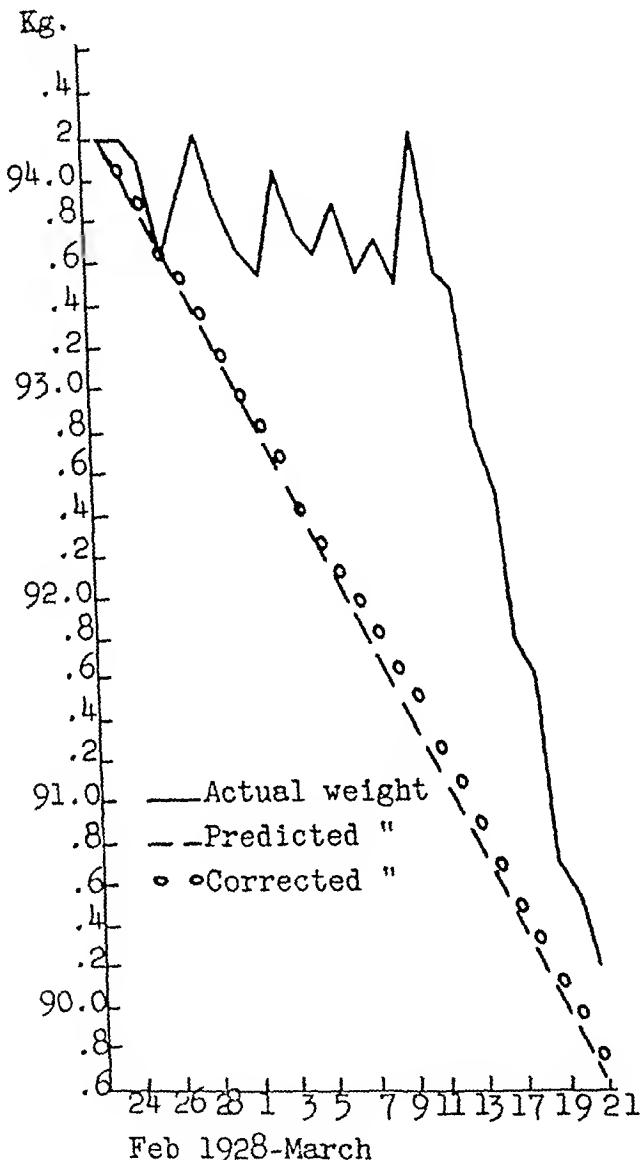


Fig. 2.

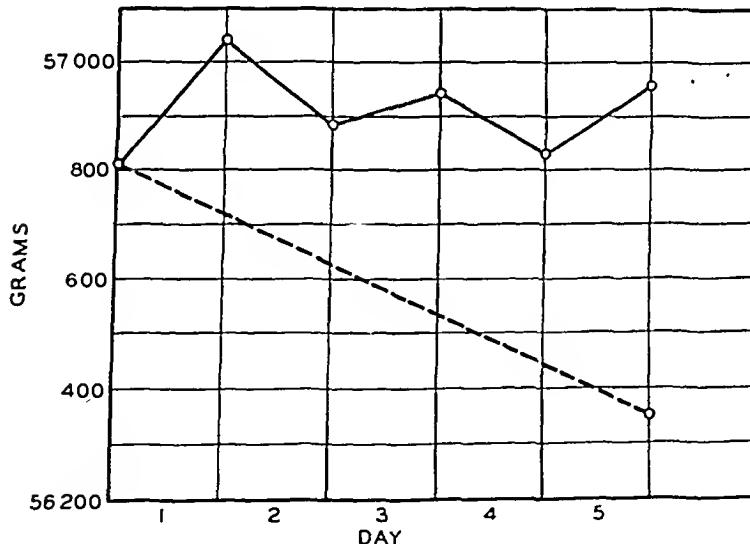
In spite of a daily deficit of 1225 calories, the patient weighed as much on the sixteenth day as she did on the first day. This was brought about by a progressive increase in body water. Subtraction of the weight of the excessive water from the actual body weight each day, gave values that agreed with the values obtained, by subtraction of the weights of the tissue destroyed from the actual body weights.

TABLE VI—ENERGY METABOLISM IN OBESE PATIENTS

RETENTION OF WATER CONCEALS DESTRUCTION OF TISSUE				
Date 1929	Change in Weight of Subject Grams	Weight of Body Tissue Destroyed Grams	Water Balance	
Feb. 3	+285	90	+369	
Feb. 4	-225	90	-105	
Feb. 5	+65	90	+149	
Feb. 6	-125	90	-41	
Feb. 7	+115	90	+198	
Totals	+115	450	+570	

PARADOXICAL GAIN OF WEIGHT BY NORMAL SUBJECT

	PRO	FAT	CHO	CAL
METABOLIZED	69	86	148	1688
DIET	63	26	148	1078
SOLIDS	6	60		
BODY LOSSES	{ PREFORMED WATER	18	6	
TOTAL		24 + 66 = 90 GRAMS DAILY		



5 DAYS
ACTUAL GAIN = 115 GRAMS
TISSUE LOSS = 450 GRAMS

Fig. 3.

A normal man gains 115 grams in 5 days in spite of a daily deficit of 610 calories. The accompanying destruction of body tissue amounted to 450 grams. An addition of 565 (115 plus 450) grams of water to the body would permit the recorded gain in body weight. The calculations summarized in Table V indicate that 570 grams of excessive water had been retained by the body.

tissue being destroyed; and that in the second phase, the excessive water was excreted. Table V shows the various items that need to be taken into account in order to know whether water is being added to or lost from the organism. It should be noted that "preformed water" is that water which is an integral part of living tissue and which accordingly becomes an additional source of "free" water when tissue is destroyed. "Insensible water" is calculated from the insensible loss of weight as explained previously. The use of these methods in the study of obese patients showed that whenever weight was lost less rapidly, while they are being underfed, than predicted from the known weight of the destroyed tissue, the difference could be attributed to retention of water. Figure 2 is an example of this condition. The patient weighed the same on the sixteenth day as she did on the first one even though the daily caloric deficit amounted to 1225 calories. During the next nine days, the loss of weight was so rapid that for the whole twenty-four days, the total loss of weight closely approximated the expected loss calculated from the destruction of body tissue. The position of the circles in the diagram was obtained by subtracting the weight of the excessive body water from the actual weight. They show that the difference between the actual weight and what it would have been due to oxidation of body tissue if nothing else had intervened, is accounted for by water retention.

It is of further interest to realize that this accumulation of excessive water is not peculiar to obesity since the phenomenon occurs in normal persons who are receiving low caloric diets. Figure 3 shows that a man of normal weight actually gained 115 grams in five days even though his diet contained 610 calories less than he produced per twenty-four hours. Table VI is the water exchange during this period. Since 450 grams of body tissue had been oxidized, it would have required the addition of 565 grams of water to the body to account for a gain of 115 grams of weight. The calculations gave an addition of 570 grams of water.

These periods of water retention may last for a few or many days and may recur frequently or occasionally. In any case they are always followed by periods of accelerated water loss that rid the organism of the excessive water. In time intervals of one or several months the patients will have lost the amount of weight corresponding to the destruction of body tissue.

Conclusions: The energy metabolism of obese patients is normal per square meter of body surface. The total twenty-four hourly heat production of obese persons is greater than normal in proportion to the increased surface area. Obesity is produced by prolonged inflow of energy that is greater than the outflow. To merely maintain an established body weight, obese persons must ingest more energy than comparable persons of normal weight.

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END RESULTS OF THORACOLUMBAR SYMPATHECTOMY FOR ADVANCED ESSENTIAL HYPERTENSION*†

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THE surgical treatment of hypertension had its origin in the pioneer work of Crile,¹ Adson and Craig,² Page and Heuer,³ Peet⁴ and others, but it was not until 1940 when Smithwick⁵ first reported his clinical studies that an efficient operative procedure was made known. The method described by Smithwick and employed by him for the past nine years includes removal of the thoracolumbar chain from the 8th or 9th thoracic ganglion through the 1st or 2nd lumbar ganglion, along the portions of the greater, lesser, and least splanchnic nerves.

In a series of 375 thoracolumbar sympathectomies followed for six months to five years, we⁶ have had 38 fatalities either in the hospital or within six months following operation. In an attempt to lower this mortality rate we analyzed the status of the 38 patients who died and that of the 337 surviving patients, and arrived at a set of rules which would reduce the mortality rate to 2.5 per cent. This figure is reasonably low in view of the fact that each patient undergoes two major operative procedures and many are recognized as poor risks.

Following the lead of Keith, Wagener and Barker⁷ who graded the eyegrounds of hypertensive patients from 0 to 4 plus we have utilized a similar method for grading the cerebral, cardiac and renal status of each patient. In order to do this satisfactorily we require, in addition to a careful history and physical examination, the following studies: examination of the fundus, electrocardiography, a 6-foot heart plate, a concentration test (pitressin or Mosenthal), urea clearance, blood urea nitrogen, non-protein nitrogen and creatinine determinations and urinalysis. Intravenous urography was applied routinely in the work-

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TABLE I

RULES FOR EVALUATION OF SYMPTOMS IN INDICATIONS
FOR OPERATION

<i>Symbols Used</i>	<i>Eyes</i>	<i>Cerebrum</i>	<i>Heart</i>	<i>Kidneys</i>
0	Normal	No Signs or Symptoms	No Signs or Symptoms	Normal
1 ±	Arteriolar Narrowing	Headaches and/or Dizziness and Nervousness	Slight Symptoms and/or Slight Enlargement and Slight E.K.G. Changes	Nocturia: But Concentration 1.024 or More: Urea Clearance 75% or More
2 +	Arteriolar Narrowing and Arterio- Venous Nicking	Headaches and/or Nosebleeds and/or Occipital Headaches and/or Dizziness and Nervousness	Moderate Symptom and/or Moderate X-ray Enlargement Moderate E.K.G. Changes	Urea Clearance 40-75% Concentration 1.015-1.023
3 +	Arteriolar Narrowing and Arterio- Venous Nicking and Hemor- rhages and Exudates	Headaches and/or Nosebleeds and/or Occipital Headaches and/or Dizziness and Paesthesia	Marked Symptoms and/or Marked Enlargement and Marked E.K.G. Changes	Urea Clearance Less Than 40%; Concentration Less Than 1.015; Normal Blood Chemistry
4 +	Arteriolar Narrowing and Arterio- Venous Nicking and Hemor- rhages and Exudates and Papilledema	Stroke or Encephalopathy or Confusion	Coronary Occlusion or Congestive Heart Failure	Persistent Eleva- tion of N. P. N. to 40 Mgm. or More and B. U. N. to 20 Mgm. or More

up of the first 150 patients until one death and two marked reactions associated with the injection of dye caused us to abandon it unless there was a significant indication for its use.

In Table I we have outlined a system of rules which serve to evaluate the degree of damage present in each of the four important organs, brain, eye, kidney, and heart, as a result of the hypertensive state. Any

patient with ten or more pluses in all probability should not be operated upon.

A system such as this one, not based on mathematical data, must be interpreted in the light of clinical judgment, and it is implied that the operator has had a moderate amount of experience in the technique of thoracolumbar sympathectomy. The rules have aided us considerably and may be of help to internists and surgeons interested in the surgical treatment of hypertension.

It is very important to the surgeon and the internist to have clear-cut indications for accepting or rejecting these advanced cases for operation. It is our feeling that death occurring six months post-operatively indicates an unwise selection of patients for thoracolumbar sympathectomy. The only exception to this rule is the case in which papilledema has produced total blindness, and operation is performed to restore vision. Even when this objective is attained, it must be understood by the patient and his family that life expectancy will not be changed by this procedure.

INDICATIONS FOR OPERATION

Ocular Fundus: It may be stated categorically that in our experience no changes in the eyegrounds per se, with the exception of marked arteriosclerosis in conjunction with evidence of marked arteriosclerosis elsewhere, are to be thought of as contraindicating operation. Failing vision is in most cases an urgent criterion for operation, often in the face of other findings which ordinarily might be considered as militating against surgical intervention.

Cerebral Vessels: The status of the cerebral vessels has been the cause of great concern. Clinically attempts to predict occlusion or hemorrhage in the vessels of the brain are notoriously futile. However, in our experience aside from a persistent hemiplegia of less than six months duration, the most dependable evidence of cerebral damage, and therefore a contraindication to operation, is mental confusion, however slight, as evidenced by the usual signs of organic brain defects, particularly recent loss of memory. Such defects were most frequently seen in the presence of other signs of generalized arteriosclerosis. Parathesis, fainting attacks, dizzy spells and pounding headaches are discussed under medical indications.

Cardiac Status: In considering the cardiac status of a candidate for

sympathectomy, the most important consideration (granting a high degree of surgical competence and skillfully conducted anesthesia) is the history of functional cardiac capacity. Cardiac failure is not in itself a contraindication, but when it completely fails to respond to the usual therapeutic procedures it is an absolute contraindication. The electrocardiogram has been of value most frequently in verifying the diagnosis of recent myocardial infarctions. In such instances it has been our policy to defer operative intervention for eight weeks or longer depending on the severity and extent of the infarction. Evidence of marked left ventricular enlargement has been seen frequently and, other factors being equal, is an indication for operation. Improvement in the electrocardiographic tracing may be expected in a high percentage of cases.

Renal Status: Renal decompensation as reflected in elevated circulating nitrogenous wastes rules out the advisability of operation whatever the underlying renal pathology. In reviewing the operation and post-operative mortality data it is apparent that renal pathology as determined by elevated blood urea nitrogen above 18-20 mgm. per cent and N. P. N. above 40 mgm. per cent constitute one of the most reliable preoperative guides from the point of view of both immediate and remote prognosis in hypertensive patients. Of the fatalities, half the hospital deaths, and almost half the post-operative deaths also fell in this group. This is, of course, a gross test of renal competence, yet in our hands it has been highly reliable, especially in the absence of other gross evidence of renal damage, such as marked albuminuria, hematuria, anemia, etc. Borderline levels must be considered in the light of other findings and the surgeon has less confidence in making a decision the closer the levels are to the upper limits of normal. Poor concentration alone has not been considered a cause for exclusion. Urea clearance determinations were done routinely, but their reliability was frequently questionable due to the difficulty of adhering rigidly to the technical requirements of the test. Additional and perhaps more refined tests of renal competence would undoubtedly have revealed evidence of renal damage in other patients with established hypertension but for purposes of pre-operative evaluation their inclusion would seem to offer little of critical value. Intravenous pyelography was rarely of any value and was presently discontinued, except when clinically indicated.

In the pre-operative evaluation of the status of an organ, problems such as the following may arise: the renal concentration test may be

only 1.013, whereas the urea clearance may be 85 per cent of normal. In that case we have one test placing the kidney in a 3 plus category and the other in a 1 plus. We therefore, average the two and consider the degree of damage as 2 plus. Similarly a patient may have excellent cardiac function, that is, he may have no dyspnea, or angina after climbing three flights of steps and yet the electrocardiograms and chest plate may show moderate (2 plus) changes. It is a matter of judgment whether the patient should be classified as a 2 plus or 1 plus cardiac.

A complete blood count, a sodium amytal test (9 grains divided into three hourly doses) and a basal metabolism test are desirable but are not emphasized in evaluating the patient's status for sympathectomy. A high basal metabolic rate associated with the hypertension is suggestive of pheochromocytoma.

The response of the blood pressure to deep barbiturate sedation or the autonomic blockade, as by tetraethylammonium chloride, is a useful device for testing the capacity for relaxation of the arteriolar bed and theoretically anticipating the result. The sodium amytal test is a good indication of a probable post-operative blood pressure result but is not absolutely accurate as a prognosticator in any given case. In our series no patient was turned down solely on the basis of a poor response to sodium amytal.

The etamon test (tetraethylammonium chloride) has been studied by Poindexter and Tamagna⁸ and compared with the sodium amytal test in over fifty patients and their report is in press. In approximately 75 per cent of the cases the two tests correlated exactly while in the remaining 25 per cent there was a variation in both directions. No post-operative evaluation of the usefulness of the etamon test has been made. In a group of ninety-four patients studied by Hinton and Lord⁹ an immediate post-operative drop in pressure was obtained in a high percentage of cases that was consistent with the drop obtained with sodium amytal. However, in a significant group no consistent correlation was noted. The effect of autonomic blockade with tetraethylammonium chloride closely parallels the results obtained with sodium amytal.

Smithwick¹⁰ has stated that patients with a hospital diastolic pressure of 140 and above do not respond satisfactorily to a thoracolumbar sympathectomy. Among twenty-four males with a diastolic pressure of 140 or higher he reports twenty deaths, three slightly improved, and

TABLE II

104 PATIENTS WHOSE DIASTOLIC PRESSURE EXCEEDED 150 MM. HG.

<i>Dead</i>	22
Hospital		13 12.5%
H-V-D	9
3-11	8
18	1
<i>Follow-Up</i>	82
0-6 mos.	..	36
12	39
24	17
Inc. Op. Pro.	2
Lost	5
<i>Mean Post-Operative Diastolic Pressures</i>		
<i>Follow Up</i>	<i>One Year</i>	<i>Two Years</i>
Resting	.. 123 M.M. (39 Patients)	129 MM. (17 Patients)
Exercise	117 M.M. (35 Patients)	121 MM. (15 Patients)

one markedly improved. The results in our cases in this category are in variance with Smithwick's findings, as shown in Table II.

De Takats et al¹¹ have emphasized the importance of operation in patients under forty years of age having a diastolic pressure not exceeding 120 mm. of mercury. Our experience with the older group would seem worth recording and is presented in Table III.

OPERATIVE PROCEDURE

We place our patients in the exact lateral position with the lower leg flexed and the upper leg extended. The table is broken under the lower costal region. The tenth rib is resected subperiosteally in its entirety. The parietal pleura is then carefully reflected from the postero-lateral chest wall, exposing the diaphragm which is divided in its entirety on the operative side. Retraction of the parietal pleura sub-diaphragmatically with contained lung and retroperitoneal fat is facilitated by two large Harrington splanchnic retractors. Delineation

TABLE III

72 HYPERTENSIVES AGED 50 - 59 YEARS
SUBJECTED TO SYMPATECTOMY

<i>Dead</i>					11		
Hospital			4	55%			
H-V-D			7				
3 - 6 Months	2						
7 - 12	3						
18 - 24	2						
Lost				3			
<i>Summary of 58 Living Patients</i>							
<i>Follow-Up (Months)</i>	6	12	24		80	36	48
Patients	10	33	12		1	1	1
Resting 110—	6 60%	20 60%	8 66%		1	1	0
Diastolic							
Exercise 110—	9 90	20 60	7 58		1	0	0

of the greater, lesser, and least splanchnic nerves along the lower thoracic and upper lumbar sympathetic chain is not difficult because of the wide exposure. The greater splanchnic nerve is divided at its junction with the celiac ganglion. The chain is grasped with a long curved hemostat and carefully dissected from each intercostal artery and vein. The communicating rami are divided several millimeters from each ganglion and the chain is divided just below the third lumbar ganglion. The twelfth ganglion is usually located just above or in the substance of the diaphragm and we have repeatedly noted how attenuated the chain is between the twelfth thoracic and the first lumbar ganglion. The thoracic chain is pursued cephalad until the third ganglion is mobilized and division is carried out above it. In the majority of instances the greater splanchnic nerve has its origin from the thoracic ganglia 6th, 7th, 8th and 9th. The lesser and least splanchnic nerves are removed as the thoracic chain is mobilized. One of the interesting findings is the wide variation in the size and distribution of the nerves. The minimum operation in a series of 440 cases included 9 thoracic ganglia through the 2nd lumbar ganglion with removal of the greater, lesser,

and least splanchnic nerves. This represents about 40 per cent of the cases reported. The operative procedure is now much more extensive. In about twenty cases we have included the stellate ganglion through the third lumbar ganglion with all the splanchnic nerves. The operative procedure as we do it now includes the 3rd thoracic ganglion through the third lumbar ganglion with all the splanchnic nerves. It is obvious that the more radical the operation the higher the mortality, but also the better end results.

PRECAUTIONARY MEASURES

As a result of our experience with 440 patients subjected to the two stage thoracolumbar sympathectomy during the past five and a half years, or from February, 1942, to August, 1947, certain principles of management during the operative and post-operative periods have evolved. These patients need every possible support to bring them through without a serious complication either due to their disease for example, coronary occlusion, heart failure, cerebral accident or renal failure or to a complication of thoracotomy such as pleural effusion, pneumothorax, atelectasis or pneumonia.

There are two basic problems to be handled during the operative and early post-operative periods: first, the maintenance of an adequate blood pressure, thereby avoiding a marked systolic fall to levels of 100 mm. of mercury or lower, which may occur with alarming suddenness, especially during and after the second stage procedure; and secondly, the management of the thoracotomy during and after operation. The maintenance of a relatively stable pressure has been best achieved by the use of 2 cc. of a 1 per cent solution of neosynephrine in 1000 cc. of 5 per cent glucose in distilled water administered intravenously during the operation; and post-operatively, by using the same fluid with 1 cc. of neosynephrine per 1000 cc. of solution until the systolic blood pressure has become stabilized at 90 or 100 mm. of mercury or higher. This may take only a few hours or it may take as long as forty-eight hours. Before this method was introduced by Milton C. Peterson, head of the Department of Anesthesiology of the New York Post-Graduate Hospital, the anesthetist injected intramuscularly or intravenously 2 or 3 minims of neosynephrine when necessary and the same procedure was used post-operatively.

We have found that a moderate anemia develops after each stage of

the extensive sympathectomy, probably due to oozing into the extra-pleural and intrapleural spaces during the early post-operative period. For this reason a 500 cc. blood transfusion is routinely administered immediately after each stage.

The second major problem is to secure hemostasis and to deal with the open thorax during the operation and to prevent serious hemothorax, pneumothorax, atelectasis, and pneumonia post-operatively. Grimson¹² has recently stated his position as follows: A closed anesthetic system is employed only occasionally using an intratracheal tube. The pleural cavity is deliberately entered through a partial 3rd rib resection and longer 10th rib resection and the chain removed from the stellate ganglion through L-1 and L-2 inclusive, followed by the use of a closed tube suction drainage of the pleural cavity for two or three days. We have also made use of a closed anesthetic system usually with an endotracheal tube. Recently we have begun a series without such a tube and the management in the hands of experienced anesthetists has been for the most part satisfactory. One point should be emphasized; this extensive sympathectomy should be carried out only when an anesthetist thoroughly familiar with open chest operative procedures is conducting the anesthesia. Although in our technique the parietal pleura is stripped from the chest wall from the diaphragm to the apex of the thorax it is usually torn to a greater or lesser extent so that air readily passes into the intrapleural space. The anesthetic agents used have been ether, cyclopropane, and ethylene, and their indications and contra-indications may be found in reports by Phelps and Burdick¹³ and Burdick, Phelps, and Peterson.¹⁴

Hemostasis is not a simple matter in this procedure and one of the frequent complications has been development of fluid in the chest post-operatively. Grimson has had a similar difficulty by his method of approach. In addition to the clamp and ligature, there are at one's disposal temporary pressure on the venous bleeder against the vertebral column, which is often satisfactory; silver clips, oxycel and other hemostatic absorbable agents, bone wax and finally the electrocautery. We have not used the last mentioned because of the fear of an explosion in the presence of such potentially dangerous anesthetic agents and the open pleura. The most serious difficulty with hemorrhage is presented by an accidental tear of an intercostal artery high in the chest cavity such as the 3rd, 4th, or 5th. When hemostasis has been secured follow-

ing the removal of the sympathetic chain and suture of the diaphragm, the chest wall is closed around a large rubber catheter placed into the pleural space. Air is completely aspirated, the catheter removed and the skin closed without drainage.

During the entire post-operative period, but particularly during the first forty-eight hours, careful, repeated, bedside examination of the chest must be made. Signs of fluid and/or atelectasis (usually due to fluid) are promptly checked by a portable x-ray of the chest and aspiration with a large (number 15) needle carried out. In patients with poor cardiac reserve pleural effusion (usually hemorrhagic) may be of the gravest significance and prompt recognition and treatment may be life-saving.

RESULTS

Though only one aspect of the disease-complex is represented in blood pressure readings they are useful as measurable end points. This is especially true of the diastolic pressure. Accordingly, we have summarized the results in 164 patients first by considering only the diastolic pressures, and by arbitrarily dividing our patients into two groups, those whose post-operative diastolic pressures were below 110 mm. Hg. and those whose diastolic pressures were above 110 mm. Hg. From this point of view, those in the latter group were considered to have a less than satisfactory result. Of the 164 patients followed for one year 93 had diastolic pressure of 110 or lower and 71 a diastolic pressure of above 110. A somewhat more dramatic response is demonstrated in the exercise column and is more steadily maintained for a longer period. We have been impressed by the number of patients whose post-operative diastolic blood pressure falls sharply after exercise, even when their resting pressure has been at higher levels. That this does *not* necessarily represent a good parallel with the effect to be expected from everyday stress and strain was apparent from the fact that frequently such sharp drops were seen in patients whose blood pressures, taken immediately after their walk or taxi ride to their appointment, were at higher levels. However, this paradoxical effect carries with it implications of benefit in those patients in whom vascular accidents might be anticipated when subjected to unaccustomed physical strain. The mechanism of such a drop in pressure may well be the result of peripheral dilatation in the muscle bed, unopposed as in the intact organism, by splanchnic con-

striction, thus averting the customary summated response of blood pressure elevation, as in the routine pre-operative response to exercise. The distribution of diastolic pressure drops, which is indicated in Table III demonstrates the significant difference between the resting and exercise results six months following sympathectomy.

RESULTS IN 104 PATIENTS WITH PRE-OPERATIVE DIASTOLIC PRESSURES ABOVE 150 MM. HG.

A review of 104 patients whose pre-operative diastolic pressures consistently ranged above 150 mm. Hg. is detailed in Table II. In this group, as might be expected, the immediate hospital mortality is significantly increased. The total number of deaths in the follow-up period at hand is high, but such an insignificant group has been followed for less than six months that further conclusions must be deferred. The range of diastolic pressure results is so broad as to preclude critical analysis from the point of view of pre-operative prognosis.

That relatively advanced age is not necessarily a contra-indication to thoracolumbar sympathectomy is readily appreciated in reviewing the data in Table III which represents the operative results in a group of 72 patients from 50 to 59 years of age. The hospital death rate was lower than that of the group as a whole, and the two-year follow-up reveals a large percentage of the patients continuing to maintain a satisfactory diastolic level. Though this group would ordinarily be expected to include a higher percentage of patients with chronic vascular changes, intensive clinical study was undertaken to eliminate those with such changes and undoubtedly the results in this group are highly colored by fortunate clinical pre-operative evaluation.

TOXEMIA OF PREGNANCY

We do not have at hand the data in a sufficiently adequate series to formulate an opinion on the relation of hypertension to the toxemia of pregnancy and the operative results. Of interest, however, are two young women in their early twenties, one with well documented hypertension of undetermined etiology, who following operation went through a full term pregnancy with an entirely normal blood pressure. The other developed hypertension during a previous pregnancy in the course of a mild toxemia, her subsequent blood pressure being in the range of 230/140 mm. Hg. One year following the day her second

TABLE IV

SUBJECTIVE AND OBJECTIVE END RESULTS OF OPERATION

No. of Patients	Follow-Up Period (Mos.)	Subjective Improvement	Marked and Moderate Objective Improvement
215	6	163	76%
148	12	123	83%
76	18	62	81%
62	24	50	80%
152	6		123 81%
69	12		62 90%
31	18		28 90%
15	24		11 73%
8	36		8 100%

*This evaluation is based on post-operative blood pressure; electrocardiographic readings, heart X-ray, blood chemistry, urinalysis, and symptomatic improvement.

stage operation was completed she delivered a full term viable infant, having maintained a normal blood pressure throughout her pregnancy. These are, of course, isolated observations, but are noted for their clinical interest.

SUBJECTIVE RESULTS

From the clinical point of view a most important consideration in the evaluation of any therapeutic procedure is the subjective result obtained. Our experience has paralleled that of others, in that we have consistently been impressed by the subjective improvement and the disappearance of severe and often disabling symptoms irrespective of the effect on the blood pressure. In obtaining these opinions from our patients, in all instances, a nurse-technician has asked them, among other questions, "Has the operation, in your opinion, benefited you?" Many factors enter into such a personal reaction. The patients may have had such a miserable post-operative course that the natural recovery from its severe discomfort leaves them uncertain that they are now better. Less easy to discount is the almost inevitable relief from pounding headaches and a sense of "relief from tension" not unlike that sensation so often described by patients who have undergone subtotal thyroidec-

tomy for hyperthyroidism. Details of the subjective results among 215 patients are tabulated in Table IV and compared with objective improvement in 152 patients of another group.

THE OVERALL PICTURE

As noted in reviewing the older age group, the final selection of patients for operation is highly colored by what, for lack of a more suitable term, we call clinical judgment. Difficult though this is to define quantitatively, nevertheless the clinical impression of a patient, to some extent, equals the sum of the effects of the disease processes at work plus the evidence of the force of the patient's particular psychology and physiology working in opposition to the disease processes. It is a common clinical observation that there are times when the patient looks better than the chart would indicate, and vice versa. We feel that most clinicians will agree, especially in the face of equivocal or conflicting laboratory findings, that such an overall evaluation of the patient must continue to play a significant part in the final decision for or against operation.

SUMMARY

In a five-and-a-half-year period, or from February, 1942, to November, 1947, there have been 455 patients operated upon for essential hypertension and most of these patients have fallen in the advanced stages of hypertensive disease. Among these patients, there were 183 males and 272 females. The total deaths in and out of the hospital from February, 1942 to November, 1947, were 74 or total mortality of 16 per cent. The causes of deaths occurring in the hospital were in the following order: cerebral, cardiac, and renal. The out-of-the-hospital deaths are in the following order: cardiac, cerebral, and renal.

One should clearly differentiate, in evaluating the end results, whether surgery has been done for the cases in the early stages of hypertensive disease or in the advanced stages of hypertensive disease. Obviously, both the in and out of the hospital mortality changes entirely depend on which type of case one is discussing.

At the present time we feel that thoracolumbar sympathectomy has a definite place in the treatment of hypertensive vascular disease, but its role in advanced cases is chiefly a palliative procedure. The overall end results in the advanced cases of essential hypertension, will give,

both from the point of view of comfort and life expectancy, a better follow-up than surgery done for carcinoma of the thyroid, breast, stomach, or large intestine whether the carcinoma cases are early or late.

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MORPHOLOGICAL BASIS FOR MENSTRUAL BLEEDING *

Relation of Regression to the Initiation of Bleeding

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INTRODUCTION

ANY attempt to discuss menstruation engenders the feelings of humility and incompetence. The humility arises, at least in part, from the limitations which prevent giving credit where credit is due to the many investigators who have contributed to our present knowledge of menstruation and the menstrual cycle. The feeling of incompetence results partly from the inability to correlate all of the observed facts and weave them into any one completely satisfactory theory of menstruation. Therefore with the realization that this description must be far from complete and satisfactory, I have compromised by restricting the narrative to little more than what one can see happening in endometrium that has been transplanted to the anterior chamber of the eyes of a monkey. Most of the evidence supporting a morphological explanation for menstrual bleeding has been presented elsewhere,^{1,2,3} and I should like to spend the time allotted to me primarily in marshalling the evidence which indicates that regression or rapid decrease in the thickness of the endometrium initiates the chain of events leading to menstrual bleeding. However, before attempting to show where regression fits into the total picture it seems advisable to summarize the events which occur during a menstrual cycle.

The interrelated changes in the hypophysis, ovaries, blood and endometrium may be considered first. The interrelationship may be most easily followed by beginning with the degeneration of a corpus luteum or ovarian follicle. As a result of the decreased blood estrogen, the anterior lobe of the hypophysis liberates F.S.H., which causes the development of additional ovarian follicles and the secretion by them

* Given 17 October 1947 before the Graduate Fortnight of The New York Academy of Medicine.

of estrogen. Their secretion may cause the slight rise in blood estrogen at about the middle of the menstrual period. However, the maintenance of the blood estrogen at about 30 I.U. per liter until about the tenth day of the cycle must be due to three factors: 1) the significant, although decreased, secretion by the degenerating follicle or corpus luteum of the previous cycle; 2) secretion by the newly formed follicles; and 3) secretion by the "chosen" follicle of this cycle. As the "favored" follicle grows, it produces more estrogen which acts back upon the anterior lobe of the hypophysis and causes the liberation of LH and probably also luteotrophin. The former causes the final growth spurt of the follicle, ovulation and the development of a corpus luteum; the latter, probably as in the rat, causes the formed corpus luteum to secrete progesterone and estrogen. Thus, the secretory activity of the corpus luteum maintains the blood estrogen level and raises the blood progesterone level to about 75 mg. per liter of urine by the twentieth day of the menstrual cycle. Soon thereafter the corpus luteum begins to degenerate, and the concentrations in the blood of progesterone and estrogen decrease. The hypophysis responds by producing more F.S.H. to initiate a new cycle.

The changes in the blood level of estrogen and progesterone may be correlated with endometrial growth in the following way. A blood estrogen level of 30 I.U. per liter in the experimental monkey, and presumably in the human, is adequate to stimulate the amount of endometrial growth that normally occurs between the end of the menstrual period and the time of ovulation. Since the blood estrogen concentration is about 30 I.U. per liter during the few days before menstruation, as well as for a number of days after the end of the menstrual period, it must follow that the preovulatory growth is not due to an increase in the blood estrogen level but to the pre- and postmenstrual level of 30 I.U. which is high enough to induce the preovulatory growth of the endometrium.

The rise in the blood estrogen on about the tenth day of the cycle and the secretion of progesterone seem adequate to produce even more growth than normally occurs in the postovulatory period.

Elsewhere³ attention has been called to the differences in behavior of the capillaries supplying the three following zones in the endometrium: 1) the general stroma; 2) the glands supplied by basket-like capillaries; and 3) the subepithelial meshwork of sinusoidal capillaries. In

the former, the rise in blood estrogen causes an increased rate of flow and probably a sufficiently elevated pressure to produce the estrogen-induced edema described by Astwood,⁴ and Williams.⁵ The increased caliber of the basket-like capillaries around the uterine glands is apparently a characteristic response in the monkey as it is also in the rat.⁵ The behavior of the subepithelial sinusoids is still incompletely understood; it deserves further study, in part at least, because of its extreme variability which tempts one to believe that it may give a clue to other unrecognized variables.

The blood estrogen declines sharply on about the twentieth day and drops from around 60 I.U. to about 30 I.U. per liter on around the twenty-fourth day. During this period the progesterone level also drops precipitously. In the monkey comparable decreases have been induced experimentally (from 45 to 20 I.U. per liter), and the decrease in the area of the intraocular endometrial transplants parallels that which occurs in the endometrial transplants during normal menstrual cycles. It therefore seems reasonable to conclude that the decrease in the thickness or regression of the endometrial transplants is due to the withdrawal of the growth stimulus supplied by estrogen and progesterone.

The manner in which the withdrawal of the growth stimulus produces regression is incompletely understood. However, it has been demonstrated that the withdrawal of estrogen slows the rate of flow through the stromal capillaries³ and thereby reduces at least one of the forces that drives fluid from the capillaries into the stroma. This shift in the equilibrium between the fluid entering and leaving the stroma should cause a withdrawal of fluid from the stroma and endometrial regression. This may represent a part of the mechanism whereby a lowered estrogen level induces regression.

Similar measurements on the rate of flow in the basket capillaries around the endometrial glands have not been completed. Nevertheless many direct observations indicate that there is a marked reduction in vascularity and blood flow to the glands after the withdrawal of progesterone. This may be the cause of collapse of the uterine glands and, also, the mechanism by which the withdrawal of progesterone leads to menstrual bleeding.

VASCULAR CHANGES PRECEDING HEMORRHAGE

The vascular changes described immediately above occur after the

estrogen or progesterone level has been decreased. They occur also in non-primate mammals and hence are not distinguishing characteristics of a menstrual cycle. On the other hand, the two following vascular changes, relative *stasis* and *vasoconstriction*, are apparently restricted to the primates. Beginning one to five days before the onset of menstruation, there is a period of slowed circulation or relative stasis, this is followed by a period of vasoconstriction which begins 4 to 24 hours before the escape of any blood.

The *period of stasis* begins after the area of the transplants has decreased 20 to 30 per cent. The circulation in the region of the transplants supplied by the coiled arteries becomes slower and slower until the erythrocytes move so slowly in the capillaries that a condition of stasis or near stasis exists. Frequently the erythrocytes do not move for 60 to 90 seconds and a distinct bluing of the transplants is noticeable with the naked eye. The stasis apparently is caused by the increased resistance to flow resulting from the increased coiling of the arteries. The duration of the period of stasis is extremely variable. In those cycles in which 63 to 76 per cent of the decrease in the areas of the transplants occurs before menstruation begins, stasis begins at least four days before the onset of the menstrual flow. If half of the regression has been completed before menstrual bleeding, stasis is present for at least two days. If less than half of the decrease in the area of the transplants precedes menstruation, stasis occurs for less than two days, and if as little as one-fourth of the regression occurs before menstruation begins, the period of stasis is less than twenty-four hours long.

Vasodilatation, which sometimes occurs during the period of stasis, is extremely variable as to both incidence and intensity. It was not observed at all in 55 per cent of the cycles, but when present, began during the first or second day of the period of regression, before the onset of bleeding and after the area of the transplants had decreased 20 to 30 per cent. It was most marked in those cycles in which there appeared to have been an interval between the end of growth and the onset of regression. However, when growth had continued at a rapid rate until regression began, vasodilatation was not observed. Dilatation occurred in ovulatory and anovulatory cycles during the breeding season and was observed in an occasional cycle during the nonbreeding season. Vasodilatation of the subepithelial sinusoidal-like capillaries caused by activity of the a-v anastomosis has been advanced by Okkels

and his collaborators⁶ as the cause of menstrual bleeding. However, it should be reëmphasized that vasodilation was not observed in 55 per cent of the 432 menstrual cycles.¹ It therefore seems obvious that in 55 per cent of the cycles studied vasodilation could not have been the cause of menstrual bleeding.

The *period of vasoconstriction* preceding the onset of menstruation is the most striking and constant event in the menstrual cycle. It precedes every menstrual period, always beginning four to twenty-four hours before the onset of the bleeding. The coiled arteries that supply the blood to the superficial two-thirds of the transplants contract and blood may remain in the arterioles, capillaries, and veins for seconds or minutes; then the erythrocytes drain out of the arterioles, the capillaries, and finally the veins. After the vasoconstriction has begun, the superficial half to two-thirds of the endometrium receives an inadequate blood supply during the remainder of that menstrual cycle. The anemic appearance of the functional zone of the endometrium is in striking contrast to that of any other tissue. The fact that a tissue which is to bleed for about four days can be so bloodless for four to twenty-four hours beforehand and throughout the period of bleeding still seems enigmatic, even after having been observed throughout 432 menstrual periods. Within a period of one to five hours one coiled artery after another contracts until all those in the transplant are constricted. All the coiled arteries in one transplant may be contracted for two days before any in another transplant in the same eye begin to contract. The lumen is almost completely obliterated in the deepest part of the basal zone, though a few erythrocytes per minute pass the region of constriction. Distal to this region the diameter of the lumen varies between 15 and 30 micra, but the passage of only about fifty erythrocytes per minute through an artery supplying a vascular field with an area of four to seven sq. mm. must indicate constriction. When the blood flow is temporarily reëstablished, bleeding occurs. Blood escapes soon after the coiled arteries relax, and continues to do so as long as circulation persists through them.

It has previously been pointed out¹ that a number of lines of evidence indicate that a product of endometrial degeneration may be absorbed systemically during endometrial regression, and that the substance may be the cause of the constriction of the basal portion of the coiled arteries. This hypothetical substance may be in fact the

menstrual toxin investigated by Smith and Smith⁷ and this may be identical with the necrosin studied by Menkin.⁸ The latter substance when injected into endometrial transplants causes constriction of the arteries.² It therefore seems probable that the vasoconstriction is caused by this product of endometrial regression. When the local concentration of this substance decreased an individual coiled artery would no longer be stimulated to contract and therefore would relax and bleeding occurs from the weakened coiled artery or its branches. The hemorrhage would be terminated when the concentration of this product of endometrial degeneration increased in the region of the coiled artery sufficiently to stimulate it to constrict again.

TYPES OF HEMORRHAGE

Menstrual bleeding occurs when blood escapes from one of the branches of a coiled artery which has been constricted for a number of hours. Five types of menstrual bleeding were observed in the transplants: 1) blood that escapes through a break in the wall of an arteriole or capillary may form a hematoma which ruptures, or 2) it may break through the uterine epithelium and escape into the anterior chamber of the eye without forming a hematoma; 3) diapedesis may occur through the wall of a capillary and the escaping blood may or may not form a hematoma; 4) there may be either a direct flow or a reflux of blood from the veins in the fields of previous hemorrhage and destruction of tissue; and 5) secondary bleeding may occur from an arteriole following experimentally induced fright or violent movement. A detailed description of these five types of bleeding in the transplants has been presented elsewhere,¹ and it should suffice here to reemphasize (a) that bleeding occurs only when the basal portion of a coiled artery relaxes and (b) that the individual hemorrhages are arrested when that portion of the artery again constricts. One of the most spectacular events one can witness is the hemorrhage from a naked artery protruding above the surface of the endometrium and the termination of the hemorrhage when the basal part of that artery constricts.

RELATION OF REGRESSION TO INDUCTION OF MENSTRUAL BLEEDING

It has already been pointed out that regression is the first of the events which precede menstrual bleeding in both ovulatory and anovulatory menstrual cycles. The length of the period of premenstrual

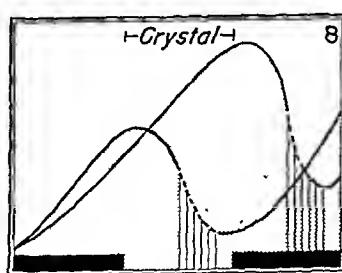
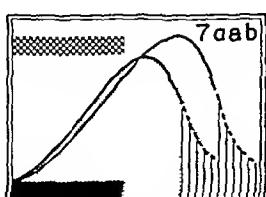
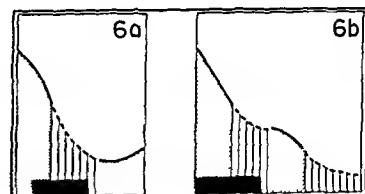
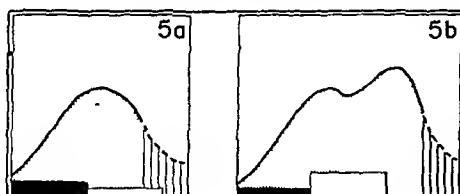
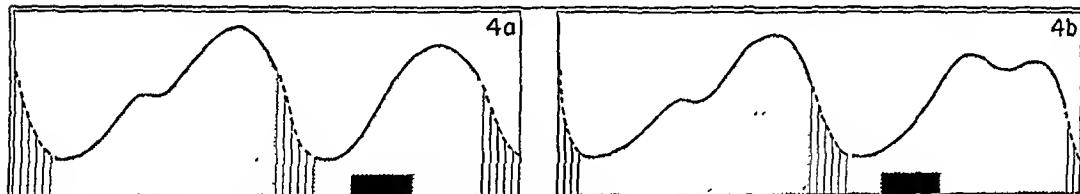
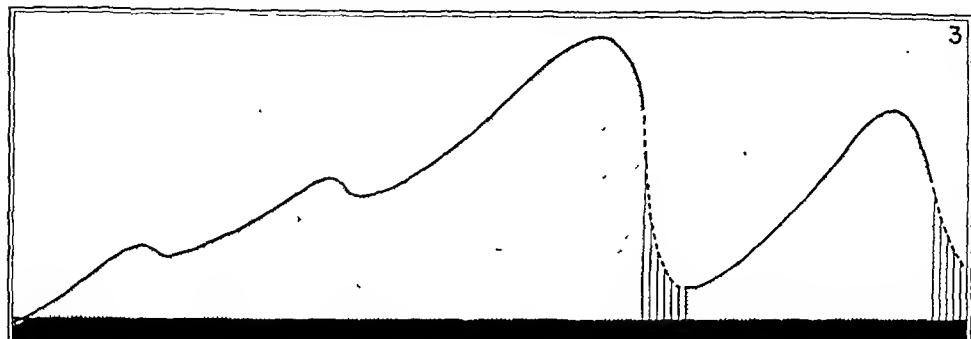
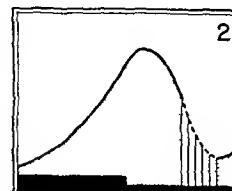
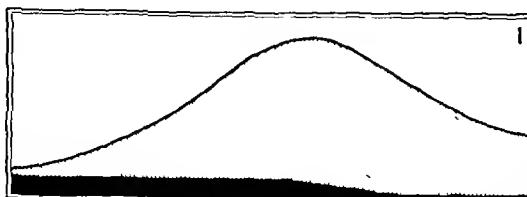
regression and the amount of regression that precedes bleeding varies in different cycles (25 per cent to 76 per cent). However, in general, the transplants that have grown most regress most, and the rate of regression is greatest in them. Since in all spontaneous cycles regression always precedes menstrual bleeding, the following eight types of experiments (Fig. 1 to 8) were carried out in an attempt to elucidate some of the relations between regression and menstrual bleeding.

I. *Induction of Slow Regression Without Menstruation.* Gradual regression without menstruation was induced by injecting about 250 R.U. of estrone a day and then gradually decreasing the daily dose to about 25 R.U. When the dosage is reduced by about 1/20 per day a slow regression without menstruation may be induced (Fig. 1).

It was found that slow regression of the transplants and of the uterus without menstruation could be induced by gradually decreasing the daily dosage of estrone, but slow regression without bleeding also occurred in uninjected and apparently normal monkeys without menstruation during periods of amenorrhea. It is possible that these periods are caused by a very slow decrease in the estrone level, as they resemble the experimentally induced slow regression not associated with menstruation. That variations in the estrone content occur during amenorrhea in woman was reported by Fluhmann.⁹ The present experiments demonstrate conclusively that time is extremely important in the response of the uterus to estrone and that the injection of a constant amount of it continues growth rather than maintains the endometrium at constant size.

II. *Menstruation Induced by Halving the Estrogen Level.* Since gradually decreasing the daily dosage produced a slow regression without menstrual bleeding, the size of the transplants were measured and graphed in experiments during which the daily dose of estrogen was suddenly decreased by 50 per cent (Fig. 2). Decreasing the daily injection of estrogen from 250 to 125 R.U. induces rapid regression of the endometrial transplants and bleeding in them that is indistinguishable from that following complete estrogen withdrawal. It should be emphasized that in this experiment only one-half as much estrogen was withdrawn as in the previous experiment but that it was withdrawn suddenly rather than over a period of eighteen days.

III. *Menstruation During a Long Series of Injections of Estrogen.* Menstruation will occur during a long series of injections of estrogen.



PROGESTERONE

ESTRONE

ESTRADIOL DIPROPIONATE

BLEEDING

ENDOMETRIUM

(SEE NEXT PAGE FOR LEGENDS)

Bleeding under these conditions was reported in the rhesus monkey by Corner,¹⁰ Hartman,¹¹ and Engle, Smith and Shelesnyak,¹² and in man by Werner¹³ and by Bowman and Bender.¹⁴ The transplants were, therefore, observed during a long course of daily injections of estrone to determine whether this bleeding was preceded by regression and the other events which normally precede menstruation and in what respects, if any, they differed from the normal. Figure 3 illustrates the change in the area of endometrial transplants during a series of 93 daily injections of 250 R.U. of estrone. Slight regression occurred on days 15 and 34 and marked regression on days 64 and 82. In this and other similar experiments¹ slight or slow regression is not followed by menstruation, but rapid and extensive regression did precede every period of menstrual bleeding that occurred during a long series of injections of estrogen.

In this experiment, fluctuation in the estrogen level was eliminated as a causative factor in the menstrual bleeding. In this experiment, as in previous ones, rapid regression appears to be the first of the sequence of events leading to menstrual bleeding.

LEGENDS

Figures 1 to 8 illustrate the relation between rapid endometrial regression and menstrual bleeding.

Fig. 1. Slowly decreasing the estrogen dosage by 9/10 is not followed by menstrual bleeding.

Fig. 2. Rapid decrease of the estrogen level by 1/2 is followed by rapid regression and bleeding.

Fig. 3. The menstrual bleedings that occur during a long series of estrogen injection (93 days) are preceded and accompanied by rapid endometrial regression.

Fig. 4. When the end of a series of injections of estrogen during the primary growth period is followed by rapid regression, bleeding occurs (a) but in this phase of the cycle menstruation does not follow estrogen withdrawal in the absence of rapid endometrial regression.

Fig. 5. Estrogen withdrawal bleeding does not occur during a subsequent series of injections of progesterone if enough pro-

gestrone is injected to continue endometrial growth, (b) but does occur if the dosage of progesterone is inadequate to prevent rapid endometrial regression (a).

Fig. 6. If the estrogen injected during menstruation and its withdrawal is followed by further rapid regression a secondary period of bleeding occurs (b).

Fig. 7. Although the interval between the withdrawal of different kinds of estrogen varies (estrone in lower curve and estradiol dipropionate in upper curve), the interval between the onset of regression and bleeding appears to be fixed.

Fig. 8. The lower curve indicates that the transplants in the untreated eye responded to the systemic changes in estrogen. The upper curve illustrates the growth of the transplants in the eye into which crystalline estrogen had been inserted and the rapid regression and bleeding of the transplants in that eye after the removal of the crystalline estrogen.

IV. Injection of Estrogen During the Primary Growth Period. In six experiments the growth of the endometrial transplants was followed after the injection of estrogen during the primary growth period (day 7 to 14). In all six monkeys the injection of 250 R.U. of estrone a day during the second quarter of the menstrual cycle caused more growth than usual and nearly as much as normally occurs near the end of the cycle.

Withdrawal of estrone was followed by regression which was slight after little, but extensive after marked growth. Estrone withdrawal terminated the growth and menstrual cycles under way, and whenever its withdrawal was followed by slight regression and arrested growth no bleeding was induced (Fig. 4b) but when regression was rapid and extensive, menstruation preceded a new cycle of growth (Fig. 4a). When it was slight the intermenstrual interval was lengthened to fifty, thirty-seven and forty-four days, but when it was extensive bleeding occurred in six to eight days.

These experiments supply additional evidence indicating that 1) endometrial regression is not always followed by menstruation and 2) menstruation occurs only when regression is rapid and extensive.

V. Bleeding After the Withdrawal of Progesterone. If a series of injections of progesterone is begun immediately after the withdrawal of estrogen, the bleeding which usually follows the withdrawal of estrogen may or may not be prevented. In a series of eight experiments graded doses of estrogen were followed by graded doses of progesterone (two examples are shown in Figure 5a and b). When the amount of progesterone given following the last injection of estrogen was large enough to cause the continuation of endometrial growth, menstruation and all the usual evidences of imminent menstrual bleeding were inhibited as long as the injections of progesterone were continued. On the other hand, when the dosage of progesterone was inadequate to continue the growth caused by the estrogen, regression was the first of the events leading to menstruation during the injection of progesterone. These experiments certainly do not throw any light on the question of the relative roles of estrogen and progesterone during the menstrual cycle. However, they do indicate that menstruation is initiated by rapid regression rather than by either of the ovarian hormones.

VI. Injection of Estrogen During Menstruation. If large amounts

of estrogen (250 to 500 R.U. per day) are injected during menstruation, the bleeding may occur without apparent alteration (Fig. 6a), or regression may be slowed (Fig. 6b). The latter happened in five out of nine such experiments. The regression which normally occurs during bleeding was slowed, and a second period of regression and an estrogen-withdrawal bleeding occurred after the injections of estrogen were discontinued. The explanation of the secondary bleeding following the withdrawal of estrone, when regression is slowed by injections of it just before and during menstruation, is suggested by the following observations. Since the straight arteries supplying the basal portion of the transplants carried more blood during estrogen delayed regression than in normal menstrual periods, it is possible that the greater amount of blood supplied to the basal portion of the transplants caused the delay. The second observation which may be related to the delayed regression is the growth of some of the dilated straight arteries and the differentiation of some of them into coiled arteries. Moreover, whenever regression was re-initiated, new coiled arteries formed from the straight ones in the basal bed, and menstruation ended when there was an increased blood flow through the basal vessels. The appearance of this phenomenon in different transplants in the same animal was as variable as the time of onset of the vasoconstriction. Since the injection of estrone during the primary bleeding caused increased circulation in the basal vessels, regression was slowed or arrested and less tissue destroyed, but regression was resumed after the withdrawal of estrone; additional coils formed in some arteries which had been spared; stasis and further destruction of tissue occurred; and blood escaped from the injured vessels. These observations may explain the secondary bleeding.

INJECTION OF PROGESTERONE JUST BEFORE AND DURING MENSTRUATION

In a series of eight experiments the injection of progesterone was begun after changes in the endometrial transplants indicated that menstruation was about to begin (the events which enable one to foretell menstruation are described elsewhere¹). In these experiments the first injection was given six, eight, eight, nine, thirteen, fifteen, sixteen and nineteen hours before the beginning of menstruation, and the dosage ranged from 2 to 10 mgm. of progesterone per day. The smaller doses had no apparent effect on the menstrual bleeding. However, the larger doses slowed regression and shortened the menstrual periods. In these

instances a period of withdrawal-bleeding began four to six days after the last injection of progesterone.

These facts demonstrate the intimate relationship of menstrual bleeding and endometrial regression. They indicate but do not necessarily prove that regression causes menstrual bleeding. It is still possible that both regression and bleeding are caused by a common factor or that a hypothetical substance which may cause menstrual bleeding can do so only during regression. Regression causes a disproportion between the length of the coiled arteries and the thickness of the endometrium, and this in turn appears to cause the development of additional coils, increase the resistance to the flow of blood through these arteries, and result in stasis which may cause the degeneration of the functional zone of the endometrium. Constriction of the coiled arteries does not appear to be related to the causation of menstruation but instead appears only to control blood loss from the damaged vessels.

VII. *Comparison of the Effect of Different Kinds of Estrogen on Withdrawal Bleeding.* An additional means of critically checking the hypothesis that regression is the phenomenon initiating the chain of events leading to menstrual bleeding was made available by the finding that in the rabbit regression is delayed longer after the last injection of estradiol dipropionate (Ciba) than after the injection of estrone. Therefore, if in the monkey an equally long interval were to elapse between the last injection of estradiol dipropionate and the beginning of regression, and yet if bleeding were to begin as soon after estrone withdrawal, menstruation should commence before the onset of regression.

Consequently three groups of monkeys, six in each group, received estradiol dipropionate. Instead of disproving the hypothesis, all eighteen experiments resulted as follows: menstruation began ten to thirteen days after the withdrawal of estradiol dipropionate, that is, four to nine days later than after withdrawal of estrone (Fig. 7). The following evidences of regression were observed in each of the eighteen experiments: decrease in the swelling and color of the sex skin; decrease in the intensity and distribution of the "washboarding"; a variable decrease in vaginal desquamation; increased coiling and buckling of the coiled arteries; venous and arterial stasis with or without vasodilatation; leukocytic infiltration; and finally vasoconstriction.

The most striking characteristic of all eighteen experiments is the

markedly delayed onset of endometrial regression after the withdrawal of estradiol dipropionate. Furthermore, the amount of delay in the bleeding in all these experiments was identical to the amount of delay in the onset of regression, the bleeding beginning about as soon after the onset of regression in the monkeys treated with estradiol dipropionate as in those from which estrone had been withdrawn. Therefore, these experiments supply further evidence indicating that extensive and rapid regression is the phenomenon which initiates the chain of events leading to menstrual bleeding. The next experiments to be reported demonstrate that when regression is induced only in the transplants in one eye, bleeding occurs in them, but not in the transplants in the other eye or in the uterus. If regression and menstrual bleeding are due to a common factor, that factor must act locally, since menstruation may occur even though the systemic estrone level is being raised.

VIII. *Local Control of Menstrual Bleeding.* Endometrial transplants in the anterior chamber of the eyes of monkeys offer an opportunity of determining whether menstruation is caused by systemic changes or by local changes in the endometrium. By introducing a crystal of estrone into one eye of a monkey which had transplants in both eyes it is possible to expose the transplants in the two eyes to different concentrations of estrogen. Those conditions permitted three types of experiment: 1) the concentration of estrone may be raised in one eye; 2) the systemic estrone level may be decreased while the crystal maintains a high concentration in one eye; and 3) the relative concentration in one eye may be decreased by the removal of the crystal, while the systemic level is being raised.

In the first type of experiment a crystal of about 0.6 mgm. of crystalline estrone was introduced into one eye of an ovariectomized monkey whose uterus and transplants had reached a base level. About four times as much growth occurred in the transplants in the eye containing the crystals as in the other eye but sufficient estrone entered the systemic circulation to cause some growth in the transplant in the other eye and in the uterus. The second and the third type of experiment may be carried out on the same monkey as follows (Fig. 8). At the end of a series of injections of estrogen a crystal of estrogen may be introduced into one eye. The transplants in the untreated eye and the uterus regress and bleed because of the lowered systemic estrogen level. On the other hand the transplants in the treated eye continue to grow. In the

third type of experiment the relative concentration in one eye may be decreased by the removal of crystals, while the systemic level is being raised by the injection of estrogen (Fig. 8). Under these conditions the transplants in the untreated eye and the uterus grow but the transplants in the eye from which the crystals have been removed regress rapidly and menstruate.

Failure of menstruation in the transplants in the eye containing the crystals while it is occurring in those in the other eye and in the uterus, owing to the lowered blood estrone level, may be interpreted in at least two ways. If menstruation is caused by a specific bleeding substance or hormone, the failure of such transplants to bleed may be due to a "protective" action of the high concentration of estrone in that eye; or, if it is due to local action during regression or to some local change caused by regression, the transplants may fail to bleed merely because they are growing rather than regressing.

Menstruation in transplants in the eye from which the crystals of estrone had been removed while the transplants in the other eye and the uterus were growing cannot be explained by a specific substance or hormone which causes bleeding, for the level of estrogen in the blood was rising. The stimulus for the bleeding in these transplants must be a purely local one, for the removal of the crystals suddenly decreases the concentration of estrone in that eye, although the systemic level is being raised by the estrone injected subcutaneously. The endometrium may be made to grow or regress, and to bleed when the systemic estrone level is rising or falling, but bleeding occurs only in those areas in which there is rapid and extensive regression. If these experiments be considered by themselves, it would be permissible to attribute the experimental bleeding to local deprivation of estrone, but menstruation can be induced in other ways, such as by the withdrawal of the corpus luteum hormone and by spinal transection. The factor that seems to be common to menstruation in transplants and uterus, no matter how induced, is rapid local endometrial regression, which it seems logical to assume is the phenomenon which initiates the chain of events leading to degeneration and bleeding. If this be correct, inquiry into the restriction of menstruation to primates need not be directed to a specific bleeding hormone, but to something that happens during regression in the endometrium of only the primate uterus.

In the primate during local regression the endometrium becomes

thinner more rapidly than the coiled arteries shorten. A disproportion hence develops and apparently is the cause of the further coiling, stasis, degeneration, and bleeding. Since the constriction of the coiled arteries preceding the onset of bleeding appears sufficiently intense to cause degeneration and bleeding, one theory of the causation of menstruation has been based on that observation. However, even when menstruation was induced in only the transplants in one eye, marked degeneration preceded the vasoconstriction and it appeared that the degeneration was caused by stasis and that the vasoconstriction, preceding and accompanying bleeding, merely prevented the excessive loss of blood from already weakened vessels, for after the onset of vasoconstriction bleeding occurred except when all the coiled arteries were contracted.

SUMMARY

Eight lines of evidence are presented which indicate that rapid regression is the phenomenon which initiates the chain of events leading to menstrual bleeding.

1. If the estrogen level is slowly decreased by 9 to 10, a slow regression occurs that is not accompanied by menstrual bleeding.
2. If the estrogen level is suddenly decreased by 1 to 2, rapid regression and bleeding occur.
3. The menstrual bleedings that occur during a long series of injections of estrogen are preceded and accompanied by rapid regression.
4. When the end of a series of injections of estrogen during the primary growth period is followed by rapid regression menstruation also occurs.
5. Estrogen withdrawal bleeding does not occur during a series of injections of progesterone if enough progesterone is injected to continue endometrial growth, but does occur if the dosage of progesterone is inadequate to prevent rapid endometrial regression.
6. If the estrogen injected during menstruation slows regression and its withdrawal is followed by further rapid regression a secondary period of bleeding occurs.
7. When comparable amounts of growth have been induced, the interval between the withdrawal of different kinds of estrogen and the onset of bleeding varies; the interval between the onset of regression and bleeding appears to be fixed.

8. It is possible to cause continued growth of the transplants in one eye during systemic estrogen withdrawal and also local regression and menstrual bleeding in the transplants in one eye at a time when the systemic estrogen level is being increased. This experiment and the preceding ones indicate that local rapid endometrial regression is the phenomenon which initiates the chain of events leading to menstruation.

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BULLETIN OF
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MAY 1948

THE USE OF RADIOACTIVE IODINE IN THE
DIAGNOSIS AND TREATMENT OF
THYROID DISEASES*

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RADIOACTIVE iodine made its appearance on the scene in 1935 shortly after the discovery of artificially radioactive isotopes by Joliot and Curie¹ in 1934. Physics thereby provided biology and medicine with a new approach to their problems—a new instrument with which to attack them.

Because the thyroid has a specific avidity for iodine, labelled or tracer, iodine obviously can be employed as a means of investigating many aspects of thyroid physiology, normal and morbid, and consequently as an aid also, in the diagnosis of certain disturbances of thyroid function. Furthermore, because we can implant, by means of radioactive iodine, a source of radiation directly within the thyroid parenchyma, one can utilize this agent as irradiation therapy in certain thyroid diseases.

It is not within the scope of the present paper to discuss the use

* From the Thyroid Clinic of the Massachusetts General Hospital.
Given 4 December 1947 at the Stated Meeting of The New York Academy of Medicine.

of radioactive iodine in the field of research, although it may be mentioned in passing that the writer at the time of its introduction, predicted that its usefulness in this field would be greater than in that of therapeutics. Now after an elapse of ten years it can be said that the usefulness of radioactive iodine in thyroid research has been firmly established, but that its position in therapeutics is still in need of more evaluation.†

DIAGNOSTIC USES

Let us first consider the role of radio iodine in diagnosis. There are three maneuvers that can be employed:

1. *Measurement of the excretion of labelled iodine* following the administration of a standardized tracer dose.
2. *Detection of the location* of administered radio iodine in the body, and its concentration by means of externally applied counters.
3. *The autoradiogram* which is the photo print of a section of tissue containing radioactive material brought in direct contact with photo sensitive film.

The determination of the excretion of radio iodine after the giving of a standard tracer dose is chiefly of use as a diagnostic procedure and as a check on therapy, in hyper- and hypothyroidism. It is a test indirectly of the avidity of the thyroid for iodine, and therefore, except when an anti-thyroid agent is operating, of the degree of stimulation of the thyroid and the kidney, and to a much less extent other tissues are in competition for it. One may assume with some degree of assurance that the thyroid takes up what iodine it requires and leaves the rest for excretion by the kidney. Both Keating, Power, Berkson and Haines³ at the Mayo Clinic, and Skanse⁴ at the Massachusetts General Hospital, have determined the curves of excretion of radio iodine following tracer doses at six hour periods up to 48 hours, at which time plateaus are usually reached. In thyrotoxic persons the excretion curves are lower and reach their plateaus sooner than in the euthyroid. The total urinary excretion of radio iodine in a 48-hour period is much less in thyrotoxic subjects than in euthyroids. In myxedema total excretion is more than in euthyroids, though the rate of excretion may be slower.

† A complete review of the use of radio iodine as a tool in the study of thyroid physiology will be found in the paper of Rawson and McArthur,² 1947.

If now we make the assumption that iodine not excreted in the urine is for the most part trapped by the thyroid, we may regard excretion tests as equivalent to tests of iodine collection by the thyroid. Keating and his co-workers⁵ have made a careful analytical study of the renal component in excretion, and have shown that impaired renal function will cause retention of iodine quite as much as trapping by the thyroid. However, from the practical diagnostic point of view, in the absence of obvious renal impairment and recent iodine medication the excretion of radio iodine can be interpreted as a dependable index of one function of the thyroid, that of collecting iodine.

Hertz and Roberts⁶ in 1942 observed the urinary excretion of tracer iodine over a 72-hour period in six classic cases of Graves' disease and in one normal subject. In the former excretion varied between 10 per cent and 37 per cent of the tracer dose, and in the latter it was 62 per cent.

At the present time the technique employed at the Massachusetts General Hospital, and devised by Dr. Skanse, is as follows:

A tracer dose of 100 microcuries of I¹³¹ (eight day half life) with 100 micrograms of inert sodium iodide as a carrier, is made up to 100 mls. One ml. is saved as a standard. The dose of 99 mls. is given orally, in the morning before breakfast, and all the urine is collected in two 24-hour periods. For the determination of the radioactivity, both of the material administered and of the urine excreted, the physician is dependent on the physicist, unless he can take the time (and it will be a long time) to become sufficient of a physicist to make them for himself. The results of the test obtained at the Massachusetts General Hospital by Skanse in three groups of cases is as follows:

1. The 48 hour excretion for 25 thyrotoxic patients varied between 6 per cent and 32 per cent, with an average of 19 per cent.
2. That for 15 euthyroid patients (controls) varied between 52 per cent and 84 per cent, with an average of 66 per cent.
3. That for six myxedematous subjects varied between 72 per cent and 91 per cent.

Such results are of course what could be expected. The hyperplastic thyroid, unless it be a frustrated hyperplasia, as when an anti-thyroid agent, thiouracil, for example, is being received, is making hormone at a rate increased over normal, and consequently must have an increased supply of iodine. In clinical hypothyroidism the converse

holds, and we find reduced collection, or indeed in full blown myxedema, no collection of iodine by the thyroid at all. Of course in full blown myxedema the thyroid may be completely atrophic.

We are asked not infrequently, which is the best index of thyroid function—basal metabolic rate, protein bound iodine level of the blood, or radio iodine excretion. Inasmuch as determination of these several values test different aspects of thyroid function, it is idle to attempt to say that any one of them is better than another. If one could always have all three, one would have a more complete picture of the morbid physiology of the patient than with but one or two. But practically, this is often impossible. Basal metabolic rate can be looked on as an index of the impact of thyroid hormone on all its end organs in the body. Its magnitude will depend both on the amount of hormone delivered and on the sensitivity of end organs to it. Protein bound iodine of the blood is an index of the level of circulating thyroid hormone and radio iodine excretion, indicating, as it does, iodine collection, is an expression of the thyroid's hunger for iodine.

In interpreting the significance of these tests in clinical cases, the points first mentioned must be kept in mind. If for convenience we speak now of radio iodine collection instead of excretion, we can say that, usually, the three values, basal metabolic rate, protein bound iodine of the blood, and radio iodine collection are all elevated in hyperthyroidism and all depressed in hypothyroidism. There are, however, some exceptions, and they are of diagnostic significance.

For example, when a hypo- or euthyroid person takes thyroid enough to produce hyperthyroidism, the basal metabolic rate and protein bound iodine are elevated, as in spontaneous thyrotoxicosis, but iodine collection is normal or depressed. Such a formula is pathognomonic of what we may call thyrotoxicosis factitia. We have detected some cases of it in persons who, being somewhat psychopathic, were taking thyroid surreptitiously. The explanation of the findings is not difficult. The basal metabolic rate is elevated because the body doesn't distinguish between an excess of thyroid hormone derived from the subject's thyroid gland, and one received per os. Also administered thyroid is reflected in the blood by elevation of protein bound iodine, as would be also autogenous hormone. But when it comes to iodine collection there is a difference between the effects of autogenous and administered hormone. When the body is flooded with thyroid hor-

mone from the subject's own thyroid, his thyroid obviously is hyperfunctioning and his iodine collection is increased. When an individual receives thyroid hormone from without, his thyroid is under no extra stimulation—indeed it may actually be inhibited, therefore his iodine collection is not raised, it may even be reduced.

Another interesting example of the diagnostic value of combined tests of thyroid function is the case of a woman with persistently elevated basal metabolism and some symptoms suggestive of thyrotoxicosis. Her radio iodine collection and protein bound iodine of the blood were quite normal. She came to autopsy finally, and proved to have a phaeochromocytoma, a hyperfunctioning tumor of the adrenal medulla. She had an excess of a calorigenic hormone which raised her basal metabolic rate, but it was adrenalin, not thyroxine, so iodine collection and hormone iodine in the blood were not elevated.

Detection of ingested radio iodine by means of Geiger-Miller counters applied to the surface of the body has been used by Hamilton and Soley as an *in vivo* technique for rough quantitation of per centage uptake by the thyroid in patients with various types of goiter. Collection curves were obtained, comparable to those got by excretion studies. Normal persons' excretion rose quite rapidly and reached plateaus in about 48 hours. The curves of thyrotoxic patients rose still more rapidly to reach peaks in about six hours. The radioactivity over the thyroid was much greater at that point than in normal subjects, but the activity then returned to about the same levels as those reached by normals.

External localization of radioactivity is also proving of great use in diagnosis in the field of thyroid malignancy. In general, thyroid tumors take up iodine in inverse ratio to their degree of malignancy. The determination of radioactivity over the surface of a goiter may give some clue to its probable nature. Also when an attempt at total thyroidectomy for malignancy has been made, this technique may be employed to determine whether any thyroid tissue remains in the neck. Metastases, if they have any iodine collecting power, and are sufficiently near the surface of the body, may be located by the counter.

The autoradiographic technique with radio iodine for studying the thyroid was introduced in 1940 by Hamilton, Soley and Eichorn.⁶ These investigators allowed sections of thyroid tissue removed surgically from patients who had received tracer doses of radio iodine to

photograph themselves by bringing them into direct contact with photo-sensitive film. By this method they were able to show that hyperplastic tissue has a greater ability to concentrate iodine than tissue from euthyroid subjects, and that cancerous thyroid tissue had little or no such ability. Leblond⁷ has modified the autoradiographic technique by making a solution of the photo-sensitive emulsion and painting it directly onto his microscopic section of tissue. In this way his areas blackened by irradiation remain in permanent juxtaposition to histologic detail. However, the histology is obscured somewhat by this process. The older method is to lay the autoradiogram over the stained sections and view them together macroscopically or microscopically.

In the field of diagnosis the autoradiogram with iodine has been exploited extensively in our clinic by Dobyns and Lennon.⁸ For over a year now the aim has been to give tracer doses of iodine to all patients coming to operation for nodular goiter. The autoradiograms of thyroid tissue so obtained add to the precision of diagnosis of thyroid function, which may be quite different in one part of the gland from what it is in another. As previously shown by Cope, Rawson and McArthur⁹ by chemical methods, there exist situations all the way from that of goiters in which a single adenoma possesses all the iodine collecting function, and the remainder of the gland none, to that of goiters in which adenomas are functionless and the remainder of the gland does all the iodine collecting. The use of the autoradiogram has facilitated, and refined this diagnostic approach. To date Dobyns and Lennon have made a total of 93 such studies. Particularly interesting is the use of the procedure to differentiate in puzzling cases between hyperfunctioning adenomas and true Graves' disease. It is also of value in the study of functioning cancers, both parent tumors in the thyroid and metastases elsewhere, if and when it is possible and proper to perform biopsies on them.

THERAPEUTIC USES

The application of irradiation to the thyroid for therapeutic purposes is far from new. Röentgen rays were so used as early as 1900, when Beck reported some observations on the Röentgen treatment of non-toxic goiter. From then on until the introduction of iodine by Plummer in 1923, the use of Röentgen rays in the treatment of thyrotoxicosis came into steadily increasing vogue. Studies on it were reported from

our own clinic in 1917 by Means and Aub¹⁰ and in 1922 by Means and Holmes.¹¹ Radium also, or radium emanation, has been implanted in the thyroid, but never became a commonly used procedure. Röentgen irradiation, of course, has long been used for cancer of the thyroid, and in certain cases still is indicated, and finally, radio iodine has been used in the treatment of thyroid diseases, both toxic goiter and cancer.

In the paper from the Thyroid Clinic of the Massachusetts General Hospital by Hertz, Roberts and Evans¹² in 1938, the suggestion was made that it was "logical to suppose that when strongly active materials are available the concentrating power of the hyperplastic and neoplastic thyroid for radioactive iodine may be of clinical or therapeutic significance."

The therapeutic effect of all forms of radio therapy of the thyroid is due to destructive action. The reduction of thyrotoxicosis depends on the knocking out, or partial knocking out, of some of the parenchymal cells. The benefit in cancer is through the killing of cancer cells.

With any of the types of irradiation used the therapeutic effect is due chiefly to the beta rays. When x-rays impinge on tissue secondary electrons are liberated which act in a beta ray like way. I¹³⁰ (the twelve hour isotope) and I¹³¹ (the eight day isotope) both emit beta and gamma rays. The gamma rays, however, are less important in the production of therapeutic effect.

For over a year now Skanse has been making studies on chicks and rats to discover the precise manner in which radiation of iodine affects the several functions of the thyroid. Briefly it may be said that when he uses in these small animals doses which in terms of the weights of their thyroids are comparable in amount of radio activity to that used for therapeutic effects in humans, he finds definite inhibition of the growth of the thyroid and impairment of its ability to collect iodine. The former effect precedes the latter. The capacity of the thyroid to respond to stimulation by thyrotropic hormone also is damaged by irradiation, but not as early as the two previously mentioned functions.

The advantages of radioactive iodine over the other forms of irradiation therapy which have been used are very great. When the thyroid collects iodine it is utilized by the thyroid cells with great rapidity, as shown by the work of Chaikoff and his coworkers,¹³ to iodinate tyrosine to diiodotyrosine. The next step in hormone manufacture, which consists in the formation of thyroxine from diiodotyro-

sine, appears to take place in either cell or follicular lumen. The point of practical importance is that very soon after the administration of radioactive iodine, most of the radio activity is to be found in the lumen of the follicle, and in delineating the mechanism involved in this type of radio therapy, one should consider that the thyroid cells are being bombarded by beta rays originating from within the follicle. This situation is greatly in favor of radio iodine as a source of radiation. Beta rays have a low penetrating power, a few millimeters, and when they originate within the follicle, the parenchymal cells, which are the desired target, are the first to be hit, nor will the irradiation travel far from the target to injure structures that it is not desired to irradiate. Contrast these relationships with those of x-rays administered from without and having to traverse the surrounding structures of the neck before reaching, or after passing, the desired target. The difference is as between shooting with a modern precision rifle and a 17th century blunderbuss.

The first reports on results of treating Graves' disease with radio iodine were those of Hertz and Roberts¹³ and of Hamilton and Lawrence,¹⁴ both of which were reported at the annual meeting of the American Society for Clinical Investigation in 1942. Hertz and Roberts gave a preliminary report on ten cases of Graves' disease treated with radio iodine, and Hamilton and Soley reported on three.

In 1946 Hertz and Roberts¹⁵ reported further on the first series of cases to be treated for Graves' disease with radio iodine. It consisted of 29 patients, all of whom were treated with the 12 hour isotope of iodine in doses varying from 5 to 25 millicuries of radio activity, given as a single dose, and followed then by a course of ordinary iodine. The reason for following the radio iodine with a course of ordinary iodine was twofold. On the practical side, it was to protect patients against mischief from thyrotoxicosis during a period in which a treatment of unknown efficacy was being tried out. I insisted on it for this reason. Also on the theoretical side it was postulated that perhaps the creating of a blood iodine barrier would retard the escape of radio iodine from the thyroid. Subsequently Chapman obtained evidence in seven cases that such an action does not appear to be exerted.

When Dr. Hertz left us for naval duty in 1943, Dr. E. M. Chapman took over the investigation of the possibilities of treating Graves' disease by means of radio iodine. First off he started a second series

of cases treated by I^{130} , the 12 hour isotope, and nothing else.¹⁶ The average dose became 30 millicuries and the range was from 15 to 79. The policy was to give from 0.5 to 1 millicurie for every gram (guessed) of thyroid tissue.

This series now includes 65 patients. At the present writing (December, 1947) 46 of these have become euthyroid, 11 hypothyroid and taking thyroid, and 8 were improved but still thyrotoxic and 5 of these were subsequently treated with a second dose, of eight day isotope. Thus far no recurrences have been observed. No untoward effects have been noted other than transient röntgen sickness, and some swelling and tenderness of the thyroid. The goiters have all got smaller and about half of them have disappeared. As to the eyes, one can say that there has been no evidence of reduction in actual proptosis, but in most instances lid retraction has been reduced, and swelling of the lids has diminished. In no instance has the ophthalmopathy been aggravated following the exhibition of radioactive iodine.

Subsequently (1946), Chapman started a third series of cases of Graves' disease in which all patients were treated only with I^{131} , the eight day isotope. The dosage used was from 4 to 14 millicuries. This series now numbers 60 patients. Of these 36 have already made satisfactory responses. Three of them had second doses given. Twelve patients are better but still somewhat thyrotoxic six months after treatment, and eleven have been treated within six months, and it is considered too early to evaluate the results. One patient died of myocardial infarction 19 days after treatment, and in one other case no follow-up has yet been secured.

At this point some discussion of choice of isotopes is indicated. For therapeutic purposes we started with the twelve hour isotope because that was the only one available. We got it from Massachusetts Institute of Technology, and with it a very generous collaboration on all the physical parts of the program from Professor Robley D. Evans and his associates. When in 1946 it became possible to get radioactive isotopes from Oak Ridge, Tennessee, MIT discontinued supplying us with iodine, but continued to collaborate on preparation of doses and detection of radio activity in excreta. From Oak Ridge we only get I^{131} , or the eight day isotope.

The dosage, of course, of the two is different. I^{130} gives off its total radiation, so Dr. Skanse informs me, in three or four days, whereas I^{131}

takes from forty-eight to fifty-six days to do so. It is obvious then that a smaller dose must be used with the latter than with the former. But how much smaller? The work of Chapman and Evans¹⁶ had shown that an effective, and not observably injurious, dose of I¹³⁰ is 0.5 to 1.0 millicurie of radio activity for every estimated gram of thyroid tissue. This dosage had become rather well established and was giving good results when we were obliged to shift to I¹³¹. Being fearful of causing some injury, the dosage employed with this isotope was in the beginning held at what was thought to be a conservative level, namely, 4-8 millicuries. It has been slowly increased to 8-14 millicuries.

The ultimate choice of isotope will depend on which offers the most benefit and subjects the patient to the least chance of harm. So far I have said nothing about harm, beyond noting that to date no serious injury has been identified. The theoretical types of harm of which we are most fearful, are the production of cancer of the thyroid some years after treatment, and injury to the kidneys caused by excretion of radioactive material. So far, no injury having been observed, it is impossible to make any choice of isotope from the point of view of likelihood of injury, nor is it yet possible to make a selection in terms of therapeutic effectiveness. It is true that to date our results with I¹³¹ are not as impressive as with I¹³⁰, but that may be merely because the method of using it is not so well developed.

In the field of cancer of the thyroid, experience is less than in Graves' disease. Our own opportunity has been greatly increased of late, however, because Dr. Rawson of our group, through the invitation of Dr. C. P. Rhoads, has been directing the studies on thyroid cancer patients also at the Memorial Hospital here in New York. In some cases neither the parent tumor nor metastases, either before or after thyroidectomy, take up any iodine, but out of 14 cases in which the distant metastases originally before thyroidectomy took up insignificant amounts of, or no iodine at all, in six after total thyroidectomy, either surgical resection or complete destruction of the goiter by radio iodine, the metastases increased in capacity to collect iodine sufficiently so that a therapeutic dose of radiation could be got into them via iodine.

In one out of three cases in which TSH was exhibited after total thyroidectomy for cancer, the metastases showed an increased uptake of radioactive iodine.

What the effectiveness of radio iodine in the treatment of cancer

of the thyroid may ultimately prove to be, cannot be foretold now. It is still in the experimental stage. Every effort should be made in all cases to make a total removal of the thyroid and its tumor by radical surgical resection. When this is impossible, all iodine collecting tissue can be destroyed by radio iodine in sufficient quantity. The great question, however, remains: can malignant thyroid tissue, by any maneuver, be induced to take up sufficient iodine to admit a total destructive dose? That at the moment is unanswerable. At least it can be said, however, we need have no hesitation in using radio iodine in the treatment of cancer as we do in Graves'. Cancer already being present, we need not worry about producing more later, nor is the evidence that renal damage may be produced sufficient to deter us. The only renal damage that Rawson has observed was in one cancer case, at the Memorial Hospital, in which, after the patient had received 180 millicuries of radiation, there was observed a 50 per cent decrease in glomerular function. After six months this returned to normal. Evidence that radio activity in thyroid or metastases injures other parts of the patient's body is lacking.

PROTECTION OF WORKERS

It would not be fitting to omit from this talk a word about the safeguarding of workers from the untoward effects of radiation. A technique must be worked out by all groups handling radioactive materials, and carried out with quite as meticulous care as is the aseptic technique of the operating room. There is this difference, however, the aseptic technique is for the patient's protection; the radiation protective technique is largely for the protection of the worker. Rules for health protection in handling radio isotopes have been issued by the Atomic Energy Commission* and should be followed insofar as the local situation demands, in any laboratory or clinic using such materials.

In our clinic at the present time here is what happens. Shipments of radio iodine are received by air mail from Oak Ridge, Tennessee. The material is in watery solution and each bottle of it is enclosed in an inch thick lead cylinder. These in turn are encased in strong wooden containers, all of which belong to the Government and have to be returned immediately. Such newly arrived material, or "hot stuff," is handled in appropriate glassware either at the end of strings or with

* U. S. Atomic Energy Commission, Isotope Branch Circulars B1 and B2, Oak Ridge, Tennessee.

tongs. All pipettings, etc., are done by distant control behind lead screens. An aliquot of all consignments from Oak Ridge is taken, duly screened to Massachusetts Institute of Technology for calibration. When this has been done, doses are made up by suitable dilution.

Doctors and technicians wear rubber gloves and lead impregnated aprons. They also wear badges containing x-ray film. Development of the film at stated intervals permits the exposure of the wearer to be measured; "0.1 rem. represents the total additive exposure from independent components of all radiation involved." Total exposure of an individual per day should not exceed this amount. Our people, we find, are not exposed to anywhere near this. Because of the concentration of iodine in the thyroid, the protection of radio iodine handlers is facilitated by examining their thyroids for radio activity with the Geiger-Müller counter, from time to time. We have not as yet found any activity over the thyroids of our workers.

The patient himself after the radio iodine is in him, is not a source of danger to others, at least if not closer to his neck or the location of metastatic cancer than ten feet. Also he would cease being dangerous even on direct contact after twenty-four days. His urine, however, is radioactive, and if it is collected, the specimens should be appropriately isolated.

There are fewer risks with radio iodine than with other longer lived isotopes. Nonetheless there are enough so that it behooves all concerned to take proper precautions.

COMMENT

It is not necessary for me to summarize or discuss further either the diagnostic use of radio iodine or the treatment of cancer by means of this agent. I am sure, however, that you expect from me at this time an opinion on the value of radio iodine in the treatment of thyrotoxicosis—how it compares with that of other types of therapy.

It is my belief that there is only one sound way to treat hyperfunctioning adenoma of the thyroid. That is surgical removal after proper preparation. Our problem, therefore, is restricted to the thyrotoxicosis of Graves' disease. In Graves' disease there is not always an indication to treat thyrotoxicosis at all. In certain phases of it there may be no thyrotoxicosis, and under such circumstances the indications may be, particularly if the ophthalmopathy is severe or progressing,

to give thyroid.

When, however, thyrotoxicosis exists and presents an indication for treatment, then we need to know which offers the patient most—surgery, prolonged antithyroid drug therapy, or treatment by means of radioactive iodine.

I may say at once that for such a purpose, were there no fear of doing injury, treatment with radio iodine would be by all odds the best therapy. Its advantages are several. From the patient's point of view it is delightfully simple—one swig of a nearly tasteless watery solution. Hospitalization is usual for preliminary study of the case, but it is not necessary as far as therapy goes. There is no necessity for frequent and close surveillance for toxic side effects as is imperative in the prolonged use of antithyroid drugs. There is not the ordeal of an operation.

To what degree the doctor should worry about late untoward effects, no one at present can say. The proponents of radio iodine therapy brush them off quite light heartedly. The very fearful refuse to use the treatment at all. If one asks experts on the effect of irradiation on tissue as to the likelihood of late carcinogenesis, one gets different replies from different experts. One such expert, in whose wisdom I have much confidence, told me he wouldn't worry about any isotope with a half life of not over eight days. My own belief is that the prospect of radio iodine induced cancer in the treated cases in the years to come is slight, but no one can legitimately say that it is non-existent.

Under these circumstances I can perhaps best indicate to you my opinion as to the relative merits of forms of therapy for thyrotoxic Graves' disease by telling you how we are actually treating our patients at the present time.

First I may say we are treating none by prolonged use of any anti-thyroid drug. Most of our patients we still treat by thyroidectomy after preparation with an antithyroid and iodine. We are committed, however, to a long term evaluation of radio iodine therapy. For that purpose we are selecting patients in the age group of 45 years or over. The idea is that if carcinogenesis does result in certain cases, it will not be before twenty or more years. Hence the selection of older patients. That is our policy at present. We stand ready to change it at any time for what seems to us good and sufficient reason.

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CRITICAL EVALUATION OF THIOURACIL AND THE NEWER RELATED COMPOUNDS IN THE TREATMENT OF THYROID DISEASE*

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Six years have now elapsed since Mackenzie, Mackenzie and McCollum¹ published in *Science* their short note on the goitrogenic action of sulfonamides. In this and in their subsequent publications in 1942² and 1943³ the Mackenzies were able to show that a number of substances including sulfaguanidine and thiourea were capable of producing hyperplasia of the thyroid gland with marked diminution in basal oxygen consumption; also that these changes were prevented or corrected by the action of thyroxin but were unaffected by increasing the content of iodine in the diet. They speculated as to the mechanism of action and came to the tentative conclusion that the thyroid enlargement was mediated by a pituitary which was receiving an insufficient supply of thyroxin from an hyperplastic but functionally inactive thyroid gland.

Their observations were confirmed and extended by Astwood and his co-workers^{4,5} who were the first to apply this newer knowledge to the treatment of human thyrotoxicosis.⁶ The development for which the Mackenzies and Astwood were chiefly responsible marked an epoch and introduced a new principle in practical therapeutics. For the first time it appeared possible to control disease by preventing with drugs the formation of a hormone.

Astwood's work attracted wide attention, and clinical data concerning the action of thiouracil, the first favored of the new drugs, accumulated rapidly and from many sources. It soon became apparent that this drug in doses which were not usually toxic could bring about a reversal of most of the undesirable symptoms of Graves' disease.⁷ Tachycardia was controlled; systolic and pulse pressure attained normal levels;

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tremor and heat intolerance disappeared; the strength of muscles was restored and normal weight was recovered. The basal oxygen consumption was reduced; the level of cholesterol in the serum rose to normal or higher than normal levels. The frequently prominent creatin defect of hyperthyroidism was no longer apparent; nitrogen and calcium balance was restored. These remarkable benefits could be attained usually without perceptible increase in the size of the thyroid gland. Of all the manifestations of Graves' disease, exophthalmos alone was not adequately controlled. Convergence was improved. The stare with its accompanying lid lag and lid spasm was diminished or lost, often giving a false impression that the proptosis had receded. Actual exophthalmometric measurements, however, revealed that the position of the eyeballs was not improved and that indeed in many cases the protrusion was slightly but definitely increased.⁸ In the presence of complications of hyperthyroidism, thiouracil was not contraindicated. The progress of thyrocardiacs and of thyrodiabetics who received the drug simulated that following thyroidectomy.

In those who could tolerate the drug, failures were few. Benefit might be prompt with return to normal conditions in a period of ten to fourteen days or might be delayed for three or even six months. Promptness of action seemed to be dependent upon the amount of pre-formed thyroxin which existed in the body at the time when thiouracil treatment was started. Large glands and those in which iodine had previously been given seemed to respond more slowly. Optimal effects were achieved early in many young individuals with small glands regardless of the original height of the metabolic rate or the apparent severity of the thyrotoxicosis. Benefit could be indefinitely continued by maintenance doses considerably smaller than those required to initiate control. Surprisingly, remissions were sustained in many patients long after the drug had been withdrawn.

Unfortunately it soon became apparent that thiouracil was a dangerously actionable drug.⁹ Eruptions, febrile reactions, or granulocytopenia appeared in approximately 10 per cent of the cases and often were sufficiently disturbing to require discontinuance. Agranulocytosis with its always alarming accompaniments occurred in about 2 per cent of all patients treated. Its appearance seemed to be independent of the size of the dose or the duration of treatment but was perhaps more frequent when the drug was renewed after temporary withdrawal or during the

simultaneous administration of sulfadiazine. It often developed with frightening rapidity, sometimes within 48 hours after record of normal blood counts. It constituted a medical emergency during which, before the advent of penicillin and streptomycin, there was a mortality of more than 10 per cent. Later when the use of these antimicrobial agents helped to prevent invasion of the body by pathogens during a crucial period, it was found that not infrequently the state of agranulocytosis was self-limited and that in many cases spontaneous return of granulocytes to the peripheral blood could be expected in ten days to two weeks, after withdrawal of the drug.

After several thousand patients with hyperthyroidism had been treated, some opinions could be expressed with considerable assurance. It was apparent that thiouracil was a very effective drug in the control of many cases of thyrotoxicosis, but that its use was limited because of toxic side reactions. The development of agranulocytosis in approximately 2 per cent of the cases was a terrifying possibility because it was unpredictable, might occur at any time during the use of the drug, and carried a considerable mortality even with the best and promptest treatment. Frequent blood counts did not constitute a sufficient safeguard. Indeed, protection against complete development of the complication rested solely on the directions of the physician and the obedience of the patient in reporting immediately any deviation of health whether it be a cold, skin infection, or indigestion. Such supervision and the need of constant contact with a physician limited the activity of patients. Management of a large number of patients who were receiving thiouracil was a source of perpetual anxiety to the physician. After three years of experience, it was the consensus of many of those most experienced in the use of the drug that whenever subtotal thyroidectomy was permitted and feasible, operation offered a solution which was quicker, more satisfactory both to patient and physician, and with optimal surgery equally safe.

Today thiouracil has no place in practical therapeutics unless it be in the extremely rare situation where more generally applicable anti-thyroid drugs prove unsuitable and where it might be desirable to utilize thiouracil as a substitute.

Propylthiouracil. The profession owes a great debt of gratitude to Astwood not only for his pioneer work in the clinical trial of antithyroid drugs but also for his meticulous pharmacological studies of some three

hundred compounds which from their chemical structure might be expected to possess antithyroid activity.¹⁰ As one result of his investigations, he was able to suggest for clinical trial in 1945 6-N-propylthiouracil as a substance which when tested in rats appeared to possess ten times the potency of thiouracil and which when administered to twenty-nine of his thyrotoxic patients appeared to accomplish all that thiouracil could do but with no unfavorable side reactions.

If animal susceptibility had been taken as a criterion for human use, 40 mg. of propylthiouracil should have produced the same benefit as a presumably optimal 400 mg. daily dose of thiouracil. Astwood's previous experience with other derivatives of thiourea had taught him that trials in animals can not be applied too strictly to man. In the case of thiobarbital, man had proven to be three to four times as susceptible as the experimental animals. His initial observations with the clinical use of propylthiouracil led him to the belief that man was less susceptible than the experimental animals but that a dosage of 25 mg. twice or three times each day should be sufficient. Thus most of the early clinical trials by all observers were carried out at this level, which was eventually found to be inadequate in many cases. Perhaps the optimal dose has not yet been established and evidence indicates that there may be considerable variation in individual susceptibility. Astwood noted that some of his patients responded rather promptly to the relatively small doses he originally proposed. On the other hand, our present custom is to start treatment with daily doses of 200 to 250 mg. and to continue with this amount until normal conditions have been established. The requirement for maintenance must be determined for each individual. Ordinarily 50 to 100 mg. each day is sufficient, but some may require 250 mg. over long periods while others need only 25 mg.

Because of widely varying individual susceptibility, usage of propylthiouracil in these doses may occasionally result in myxedema. Astwood encountered hypothyroidism in eight of one hundred cases and on doses varying from 25 to 50 mg. per day at variable periods after the inception of therapy.¹¹ In the eighty-one cases treated in our clinic, there were four cases of myxedema, two of which were noted at the end of the period of intensive therapy. Both of the others developed while on a maintenance dose of 25 mg. which had been continued for several months following the initial intensive therapy.

Failure to control thyrotoxicosis with sufficient dosage of antithyroid

drugs, either thiouracil or propylthiouracil, is rare, and most of those reported have been in early series before sufficient experience in dosage and individual variation of response had been accumulated. Lahey¹² has recently reported his experience in the use of antithyroid drugs as a means of preparation for operation. The series included three hundred and eighty-one treated with thiouracil, twenty-eight with thiobarbital, and two hundred and sixty with propylthiouracil. He states that he encountered no patient who could not be controlled if the drugs could be given in large enough dose over long enough time. Remarkable resistance may be encountered, however, as in one of our patients whose thyrotoxicosis has failed to yield with a daily dosage started at 250 mg. gradually increased over a period of 5 weeks and now maintained for 5 months at 900 mg. of propylthiouracil.

Toxicity of propylthiouracil. Information from the manufacturers of propylthiouracil indicates that the drug was distributed for experimental trial in 3000 to 4000 patients before its commercial introduction. The number since treated cannot be estimated but is undoubtedly large. Thus far no death attributable to the use of this drug has been reported in the literature or has come to the attention of the manufacturers.¹³ In approximately 1000 cases in which details were made available to the manufacturers of the drug, no instance of agranulocytosis was recorded. Reports have appeared in the literature from Astwood concerning one hundred cases treated without serious intoxication,¹¹ from McCullagh¹⁴ in whose one hundred and ten cases there was one instance of sore throat with a fall in the leukocyte count, and from McGavack¹⁵ whose seventy-one cases included one instance of febrile reaction which led to withdrawal of the drug. In our clinic at the New York Hospital eighty-one cases have been treated without encountering intoxication sufficiently severe to require discontinuance. Since the drug has become generally available the manufacturers have obtained information concerning three unpublished cases in which the responsibility of propylthiouracil in the causation of agranulocytosis was authentically established. One other case was recently recorded.¹⁶ In a recent report, Lahey and Bartels¹² gave their experience in the use of propylthiouracil in preparing two hundred and sixty patients for surgery. In one there was a febrile reaction, in four there was mild depression of the white blood cells, and in one severe agranulocytosis was mentioned but without details.

Other undesirable but minor symptoms have been encountered. These have included urticarial eruptions, pruritis, and headache. These have seldom been of severity sufficient to require withdrawal of the drug, or to interfere seriously with the management.

It would be surprising indeed if a drug as potent as propylthiouracil did not display some undesirable side effects or produce occasional serious intoxication, and its extraordinarily favorable record to date does not preclude the possibility of latent toxicity. Its relative safety when compared with thiouracil, however, has been clearly established.

Remissions. The continuance of remissions following the withdrawal of antithyroid drugs has been much discussed. Reports in the literature are confusing since they are based on variable data concerning initial and maintenance dosage, duration of treatment, as well as the age of patients, the type of goiter and the severity of the thyrotoxicosis. Percentages of relapse in different series vary from 20 to 80 per cent. Williams¹⁷ figures are impressive from the standpoint both of the number of cases and of the length of observation. Of one hundred and eleven patients, fifty-one appeared at the time of writing to be in no further need of treatment, forty-four had maintained remission for more than a year and thirty-three for more than 18 months following the discontinuance of the drug. It was of interest that 70 per cent of the relapses occurred within 2 months and 88 per cent within 5 months of the cessation of treatment and that only one patient relapsed after remission had been maintained for a year.

In our own series of patients treated with thiouracil we reported one of the highest figures, 76.6 per cent, for sustained remissions. Continued observation of the same patients over a period of 2 more years has now reduced the percentage to less than 50 per cent.

From the accumulated data some generalizations are permissible.

The administration of thiourea derivatives does not demonstrably modify the basic etiological factors which were initially responsible for thyrotoxicosis. When such factors remain potent and active, relapses are probable and should be expected more frequently and earlier than after subtotal thyroidectomy since the amount of gland tissue which may participate is greater. It now appears that a sustained remission rate of 40 to 50 per cent following the discontinuance of antithyroid therapy may be compared with one of 80 to 90 per cent following optimal surgery. There is evidence that sustained remissions are less frequent in

men. Williams' experience is striking and showed 18 per cent of twenty-one males and 52 per cent of ninety females. Relapse appears to be more frequent in severe thyrotoxicosis and with large goiters although many exceptions may be found in the literature. In Williams' series the age of the patient, the duration of the disease and the nodularity of the goiter appeared to have little relevance to the tendency to relapse.

No rules are yet established as to the optimal duration of treatment or the time of discontinuance of the drug. Perhaps those who can be maintained in normal condition on small doses such as 25 mg. of propyl-thiouracil can continue to do well without treatment. The ability to endure difficult life situations without development of thyrotoxic symptoms should be taken into account. Enlargement of the thyroid gland with or without bruit in the absence of hypothyroidism has been emphasized by Williams as an indication for the continuance of treatment.

With the advent of propylthiouracil and with continued experience indicating the harmlessness of continued treatment, the problem becomes less serious. Perhaps it will be found expedient to continue maintenance dosage in many cases indefinitely in a manner similar to the use of thyroid in myxedema. This practice introduced during the past few months in our own clinic has been found thus far both safe and satisfactory.

Combined use of iodine and the thiouracils. There is consensus that the administration of iodine previous to the exhibition of thiourea derivatives tends to delay the benefit of the latter. Although there are many apparent exceptions where prompt response was obtained, the trend was unmistakable. The suggestion was made early in the experience with antithyroid preparations that the simultaneous administration of the two drugs might also impair or delay the action of thiouracil. This has proven to be erroneous and it is now recognized that iodine and thiouracil can be given together both in preparation for thyroid operations and in continuous treatment. Pathological studies have shown that the use of iodine permits increased colloid storage in glands made hyperplastic by thiouracil and diminishes both the vascularity and friability of thyroid at the time of operation.¹² Note has been made that simultaneous use of the two drugs may increase the size of the gland, a tendency which is seldom apparent when thiouracil is administered alone. While undesirable, such enlarge-

ment is seldom obtrusive and does not ordinarily constitute a contraindication to the practice.

It now appears that thyrotoxicosis can be controlled by derivatives of thiourea in almost all cases which do not display toxic reactions and that in the use of propylthiouracil, immediate undesirable or dangerous side actions are so infrequent as to constitute little contraindication to its continued use. Exception has been taken, however, in several groups of cases and possible dangers of long continued administration have been considered. It has been suggested that continuous use with the resultant hyperplasia may lead to the development of cancerous changes in the gland. Ward¹⁸ and Hinton and Lord¹⁹ on the basis of histological studies have proposed that every nodular goiter should be prophylactically removed with the corollary inference that antithyroid drugs should be used in nodular toxic goiter only in preparation for operation. Early studies in animals demonstrated the placental transmission of thiouracil with concentrations in placenta higher than in the blood of the mother and in the fetal blood approximately 50 per cent of the maternal hyperplastic glands amounting to goiter with later developmental defects were found in the offspring after birth. Such observations justifiably led to a fear of administering the drug to thyrotoxic individuals during pregnancy. All of these exceptions deserve critical scrutiny.

POSSIBLE CARCINOGENIC ACTION

Bielschowsky²⁰ reported in 1944 that simultaneous administration of the carcinogenic agent α -acetyl-amino-fluorene and allyl-thiourea produced adenomas and malignant tumors in the thyroid glands of rats, an effect which could not be demonstrated by the use of either drug alone.

These observations inspired an editorial in the Journal of the American Medical Association²¹ which raised the natural question as to the possibility of causing cancer by thiouracil treatment of older patients in whom some carcinogenic factor may be present. Relevant to this problem are recent experiments of Rogers, Asper and Williams²² who administered α -acetyl-amino-fluorene and thiouracil simultaneously to a series of 12 rats with resultant malignant tumors of the breast and other organs but with hyperplasia as the only detectable lesion of the thyroid gland. Possibly relevant also are the observations of Paschkis²³

who studied mitoses by the colchicine technique during administration of thiouracil. He found that mitotic activity reached a maximum in 10 to 15 days, and became less marked with continuance until after 6½ to 7½ months of uninterrupted thiouracil treatment, few mitoses were demonstrable. More impressive is the record of patients treated over long periods with antithyroid drugs. The exact number who have received one or another of the derivatives of thiourea cannot be known but must now include many thousands, some of whom have taken the drugs over long periods. Those constituting the group reported by Moore from the associated hospitals have been under rigid scrutiny and have included a large number of nodular toxic goiters. It is significant that after more than six years of experience only one case of carcinoma has been mentioned. This instance which was mentioned by Payne²⁴ of Norfolk in discussion at the 58th Session of the Southern Surgical Association deserves attention. A woman of 34 with a typical syndrome of hyperplastic hyperthyroidism received 0.6 gm. thiouracil daily for six weeks and iodine for 10 days in preparation for thyroidectomy. The removed thyroid was said to show an area of carcinoma about 3 mm. in size located in the center of both removed lobes. The gland itself was hyperplastic without nodules. The criteria for the pathological diagnosis of cancer and the type of malignant change were not mentioned although it was stated that several outstanding pathologists had agreed that the stained sections showed carcinoma. The difficulties of positive diagnosis from such small areas in a gland where surrounding cells are displaying the mitotic activity of hyperplasia must be admitted. Evidence to date does not preclude the possibility that antithyroid drugs can induce neoplastic changes but indicates that they are extremely rare or clinically insignificant.

USE IN NODULAR GOITER

In much of the recent literature there is insistence that nodular toxic goiter should be treated surgically because of the danger of carcinomatous change in thyroid nodules. This opinion has been based upon histological examination of nodular thyroids removed at operation. Thus Brenizer²⁵ in North Carolina found 4 per cent of carcinoma in 2324 cases, Ward¹⁸ in California 4.8 per cent in 3539 and Cole²⁶ in Illinois 7.2 per cent in 532. The viewpoint emphasizing the necessity of surgical removal of nodular goiter was dramatically presented by Hinton

and Lord¹⁹ who compared the incidence of clinically unsuspected cancer in nodules of the thyroid with similar nodules of the breast on the necessary removal of which there is contemporary consensus. For the breast they found 6.7 per cent of seventy-five cases, and in the thyroid 7.6 per cent of one hundred and eighty-four cases. If this comparison can be taken at face value the situation is urgent and the indication for surgical removal is at least as great for nodules of the thyroid as it is for those of the breast. There is however an obvious objection to acceptance of such a thesis. Although the histological studies of surgically removed thyroid nodules indicate a frightening incidence, clinically recognizable carcinoma of the thyroid is rare. Older statistics concerning the incidence of thyroid cancer indicate a remarkable correlation with geographical location, 1.04 per cent for the goiter district of Switzerland (Kocher and deQuervain) and approximately 0.1 per cent in non-endemic areas in the United States. Wilson's²⁷ tabulation in 1921 of 74,335 cases autopsied in this country showed an incidence of 0.26 per cent of thyroid carcinoma. This is to be compared with the incidence of nodules in the thyroid gland which may be found in 80 per cent of autopsies in a goiter area and in 8 per cent in non-endemic areas.²⁸ Rogers²² and his associates in their instructive review have calculated that by using the Cole's figure of 7.2 per cent of carcinoma in nodular goiter, one might expect more than 5 per cent of the population in a goiter region and more than 0.5 per cent in a non-endemic area to suffer from thyroid carcinoma. Their examination of diagnoses of 544,918 admissions to the Boston City Hospital, the Johns Hopkins Hospital and the Massachusetts General Hospital is illuminating. Only 74 diagnoses of malignant thyroid neoplasms were found constituting 0.0136 per cent of the total hospital admissions and 2.29 per cent of all the clinically recognized goiters.

Interesting also is the distribution of histologically recognizable malignant neoplasia in non-toxic and toxic nodular goiter. Cole's figures which indicate the most disturbing incidence, revealed 17.1 per cent in patients in the non-toxic group and only 1.2 per cent in the toxic nodular cases.

Comparison of pathological and clinical experience leads inevitably to the conclusion that a large number of the thyroid glands which appear histologically malignant do not become clinically recognizable. It also appears that the great majority even of the histologically recog-

nized cancers develop in non-toxic goiters and that the incidence even of histologically recognizable cancer is low in the toxic nodular goiter which is the point of discussion in relation to the use of antithyroid drugs.

Such evidence should not lead to neglect of the possibility of the development of cancer. It indicates however the relatively small risk and a careful weighing of this risk against that of operative interference. Furthermore it must be emphasized that in relation to cancer prophylaxis, the mere presence of nodules in the thyroid may be less important than the circumstances under which they occur. Nodules encountered in the glands of young people in whom the incidence is low, single nodules at any age, nodules in aberrant tissue and nodules in which recent growth has been observed should excite attention as possible malignancies and usually should receive prompt surgical treatment. Furthermore all patients with nodular goiter should be warned to report if differences in size of the gland or a portion of it are noted. Evidence at present however does not justify the dictum that all who have toxic nodular goiters should have prophylactic thyroidectomy. Indeed it appears that a large number of them can be treated safely and successfully with antithyroid drugs.

Use in pregnancy. Early fears concerning the dangers of using thiourea derivatives during pregnancy have not been justified by accumulating practical experience. Astwood reported four cases,¹¹ Williams¹⁷ saw nine patients treated for a month or more of their pregnancy. In three the drug was given before fertilization and continued throughout the pregnancy. One patient was similarly followed in our clinic. In none of these cases was the infant found to have goiter or other defect that could be attributed to the treatment. In light of the early animal experiments, however, it would appear wise to limit the dosage during pregnancy to the lowest which is necessary for maintenance of the health of the mother. Williams has emphasized the desirability of weaning infants of mothers who are taking antithyroid drugs since they are secreted in considerable amounts in the milk.

It is as yet too early to judge of the definitive and optimal treatment of Graves' disease. For many years, subtotal thyroidectomy was the only measure which offered hope of control. In the hands of the most skilful surgeons the results achieved have been favorable indeed with an operative mortality of less than 1 per cent and the prospect of per-

manent remission following thyroidectomy in well over 80 per cent of cases. Now there are two other therapeutic expedients which afford adequate control. As yet the experience with each of them is less than with surgery. Difficulties of regulating dosage with radioactive iodine have not yet been overcome. Propylthiouracil has not been tried for a sufficiently long time to judge of end results not to permit complacency concerning the absence of toxic manifestations. If it is indeed as harmless as it now appears to be, it offers an extraordinarily satisfactory method of control. In comparison with surgery and radioactive iodine, it has one outstanding and precious advantage, that of reversibility. When one takes into account the highly variable functional activity even of normal thyroid tissue, the ability to permit or inhibit the production of thyroxin to meet changing needs and life situations would appear to be a matter of importance.

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CERTAIN CONSIDERATIONS IN THE APPLICATION OF ISOTOPES TO MEDICAL PROBLEMS*

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SINCE ancient times, astronomers have studied the fixed stars and have accumulated vast amounts of information about their behaviour and composition. Within relatively recent times it has been proven that several of the stars previously considered to be single heavenly bodies are in fact made up of two discrete bodies rotating about each other. The study of such astronomical twins has been a fruitful field of investigation and has yielded information about the behaviour of stars in general, information which might have been difficult, perhaps impossible to secure had these twins not been discovered. Without in any manner supplanting the other disciplines of astronomy, the study of these twins has added materially to the general body of astronomical knowledge.

If we now negotiate the well-travelled transition from the vastly large to the vastly small, we find an analogy to the discovery of stellar twins in the discovery of similar siblings among the atoms of the elements. Associated with the names of the Curies, Moseley and Aston came the realization that the naturally occurring atoms of many of the elements were not homogeneous but were in fact mixtures. Thus, whereas the atoms of a given element were all identical with each other in regard to the number and arrangement of their planetary electrons, and hence in their reactivities, as the chemist is accustomed to use this word, the nuclei of these atoms might differ from each other. This nuclear variation manifested itself in variation in the atomic masses of the several atoms, in view of the fact that the weight of an atom is concentrated in its nucleus, and it has now been established that virtually all of the common elements, each comprising one species of atom, chemically speaking, contain two or more sub-species of atom of different mass numbers. These sub-species of atoms, siblings, if you will,

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chemically essentially indistinguishable from each other but differing in mass, are the isotopes about which we shall hear this evening.

There are certain properties of the naturally occurring isotopes which should be stressed at this time. The nuclei of the isotopes of the elements of lower atomic weight which occur in nature are in general perfectly stable, they have no tendency to decay or undergo spontaneous transmutation, and they emit no energy, whether radiant or particulate. The relative abundances of the naturally occurring isotopes of any element are extraordinarily uniform, if one examines various samples of the same element obtained from different sources. Both of these characteristics find exceptions among the heavier elements of the periodic table. The several isotopes of any element enter the same chemical reactions and at very nearly the same rates, both in the test tube and in the animal.

These in general are the properties of which the investigator takes advantage when he employs isotopes in tracer studies. In order to undertake such a study, however, there must first be made available to the investigator a supply of the desired element in which the relative abundances of the several isotopes are far from their normal abundances. In other words, the isotopes of nature must be separated. Unfortunately, in most cases this is a very laborious, and consequently a very expensive procedure. In fact, except in the case of hydrogen, where it has been found practical to separate heavy water, deuterium oxide, from light water, hydrogen oxide, as a by-product of the ordinary commercial use of water in electrolytic reactions, the expense of separated samples of naturally occurring isotopes has been a deterrent to their wide use.

The list of naturally occurring isotopes has, over the past few years, been tremendously supplemented by the generation of man-made isotopes, isotopes which, in many cases, do not occur in significant concentrations in nature. These materials today are products of cyclotrons, as in Berkeley, or chain reactors, as at Oak Ridge, and differ in one very important regard from the naturally occurring isotopes which I have just described. In general, these products are radioactive, which means, structurally, that the nuclei of these atoms, in contrast to those of the majority of the naturally occurring isotopes, are unstable. As these radioactive atoms undergo decay and transmutation, their nuclei emit radiations of the same types as have been long recognized to arise from

radium and its degradation products. Each sub-species of atom, according to its own particular habit, emits either alpha or beta rays, often accompanied by gamma radiation. Alpha particles, you will recall, are particles of mass four, doubly positively charged; beta particles are in fact electrons, of a mass approximating zero and singly negatively charged; and gamma radiation resembles visible light, only of extremely short wave-length or high frequency. Whenever an atomic nucleus emits either an alpha or a beta particle, the residue which is left behind is necessarily an atom of a species of element different from that initially present; in other words, a spontaneous transmutation will have been effected.

It is characteristic of radioactive decay that the rate at which atoms of a sample of radioactive material undergo transmutation depends exclusively upon the number of radioactive atoms present at that time. This rate appears to be uninfluenced by such variables as temperature and pressure, and ordinarily chemical operations seem to have no effect upon the probability of a particular atom decaying at a particular time. From the mathematics of the situation it may readily be shown that the time required for the complete decay and disappearance of a sample of radioactive material approaches infinity, regardless of the rate constant of this decay. In describing radioactive materials, therefore, it has been found convenient to refer to the half-life, the length of time which will elapse before half of the material initially present will have undergone transmutation. This half-life is a constant quantity for any particular sub-species of radioactive isotope, though it varies widely from one isotopic variant to another, ranging all the way from a small fraction of a second to many thousands of years, in the extreme cases. In the limiting case, stable isotopes may be regarded as having infinite half-lives.

In addition to finding a supply of concentrated isotope of the desired element, the investigator must also devise or purchase suitable equipment for the analysis of isotopic mixtures. In the case of the stable isotopes, ultimate reliance is placed upon the mass-spectrometer. In the exceptional case of hydrogen-deuterium mixtures, other methods, dependent upon some property related to the atomic mass, have been devised, but in all other cases, a mass-spectrometer is essential. This is a complex and expensive piece of electronic equipment, and, because of the cost of the commercially available units, is, in many laboratories,

of home construction. As its name implies, it distinguishes between the isotopic sub-species of an atomic species on the basis of the difference in mass.

For the analysis of isotopic mixtures containing a radioactive component, one takes advantage of the fact that the emanation from radioactive materials, whether alpha, beta or gamma, alters the electrical properties of the gas through which it is passing. Various electrical devices have been employed for the quantitative measurement of these changes, the most popular of which today is the Geiger-Mueller counter, backed by a suitable scaling circuit. Instruments of this type are widely available commercially and at relatively moderate price. Even though the precision of measure, with such instruments, is in general not so high as may be obtained with a mass-spectrometer, the availability of the instrument and ease in its maintenance and operation has resulted in many laboratories favoring the use of radioactive over stable isotopes.

One frequently overhears, among workers in the field, heated debates over the relative virtues of the stable and radioactive isotopes, and a few generalizations in regard to this argument may be appropriate at this time. Once it is decided what element is to be employed, the first question is: What isotopes of that element are available? Radioactive isotopes of more than half of all the elements in the periodic table may be obtained from Oak Ridge, whereas the list of stable isotopes that have been separated from nature in usable quantities is very brief. Of at least two elements of prime biological interest, however, no radioactive isotopes are at hand, and therefore, if one wishes to work with nitrogen or oxygen, one is forced to employ the stable isotopes which, fortunately, are available. When carbon or hydrogen is to be used, the worker has a choice of both radioactive and stable products, while with such elements as phosphorus or iodine, only the radioactive modifications can be obtained thus far.

Of the many problems to which isotopes have been applied, there are certain ones in which the radioactivity *per se* is an integral part of the procedure. In such problems obviously a radioactive isotope must be employed. The administration of radioactive materials in the hope of altering cellular processes incident to the radioactive emanation is a favored type of investigation. Among the fields in which this type of study has proven of great interest is in the control of neoplastic

processes and here the experimenter tries to take advantage of the fact that certain elements and certain compounds tend to concentrate in certain tissues as a result of the vital processes going on in these tissues. The hope in every case is that a suitable radioactive material will be found to concentrate inside the cell in which alteration is to be produced. If this is accomplished, two benefits are achieved. In the first place, injury to other tissues will be reduced to a minimum, and in the second place, in view of the extreme proximity of the source of radioactivity to the cell under study, the law of physics which relates the effective intensity of radiation to the reciprocal of the square of the distance from its source, will in good part have been circumvented. The studies which Dr. Werner will describe constitute a beautiful example of this approach.

Another type of experiment in which radioactive isotopes are essential is one which depends upon the technique of radioautography. This technique is particularly useful in studying the anatomical distribution of an element or a compound. It involves the administration of a material labeled with a radioactive isotope. Sections or blocks of tissues are then prepared and brought in close approximation to a photosensitive emulsion. With the complete exclusion of extraneous light, those points on the emulsion which are struck by emanation from decaying radioactive particles will become exposed, much as an x-ray film is exposed, and on subsequent development and fixation, will appear as black spots. Superimposition of the emulsion upon the histologically stained specimen permits the observer to ascertain at what points in the section the isotopic material which had been administered, has concentrated, because, at those points, the emulsion will be exposed. The technical details of this procedure leave a great deal to be desired, at the present time, but hopes for the future are high. It is of passing interest that the history of radioautography is really surprisingly ancient, that the earliest evidence of radioactivity was obtained by Becquerel when he noted that a sample of pitchblende produced a fogging of a piece of photographic film which was separated from it by a piece of black paper.

Yet another type of experiment in which radioisotopes are of peculiar usefulness depends upon the fact that, in select cases, it is possible to determine the distribution of a radioactive material in the body by superficial exploration of the surface of the body with a sensitive in-

strument like a Geiger-Mueller counter. Not only have the limits of the integrity of circulation in a gangrenous extremity been explored by this procedure, but the detection of metastatic tumors of the thyroid has also been accomplished in such cases where the metastasis retains the capacity to concentrate radioiodine.

In regard to tracer studies in the realm of intermediary metabolism, certain of the criteria for the selection of the most appropriate isotope for the job at hand have already been mentioned. One will have to consider the availability and cost of the needed isotope, and the nature of the accessible analytical instruments. The selection of the stable isotope of nitrogen by Dr. London, for the experiments which he will describe, was obviously dictated by the fact that no other isotope of nitrogen is known to occur.

An open choice is still available to the experimentor who requires isotopes of hydrogen or carbon. In each case both the stable and radioactive isotopes have found usefulness and the selection is often dictated by considerations other than those mentioned so far. Of the two radioactive isotopes of carbon, that of mass 11 is of limited usefulness in that its rate of decay is very rapid, its half-life is of the order of one half hour. It is suitable therefore only for experimental procedures which are completed in a relatively few hours. The isotope of mass 14 has a half-life of somewhat over 5000 years, and is therefore eminently suited for biological studies. Its great advantage over the stable isotope of mass 13 is the dilution which it will withstand before it is lost analytically. The stable isotope of mass 13 exists in nature as about 1 per cent of all samples of carbon, the remainder being the familiar carbon 12. If one starts with a sample of carbon enriched with carbon 13 to the greatest extent that has been achieved to date, and dilutes this with ordinary carbon a few thousand fold, the enrichment of isotope becomes indetectable even to the most sensitive instrument designed for its detection. The radioactive isotope of mass 14, however, may be diluted millions of times with ordinary carbon, and its concentration still measured analytically with relative ease. If therefore the protocol is one in which one may anticipate tremendous dilution of the material administered prior to its final isolation and analysis, one might be forced to select the radioactive in preference to the stable isotope.

There are assorted hazards incident to the handling of radioactive

materials, which, taken together, constitute the chief advantage of the stable over the radioactive isotopes. The most obvious situation arises from the refusal on the part of the Atomic Energy Commission to permit the use of carbon 14 in studies on the human subject at this time. This ruling is based upon the very long radioactive life of this isotope and the uncertainty of the biological duration of a carbon atom in the human body. In view of the cumulative nature of radiation injury, the authorities have come to the properly conservative conclusion with the result that, if one desires to employ isotopic carbon in human experimentation one is compelled to use the stable carbon 13. The stable material is of course free from any such restriction.

Hazards to the health of the experimentor, his colleagues, and incidental personnel such as scrub-women and plumbers, constitute a major problem. For protection from radiation injury one relies on two devices, shielding and distance. The nature and thickness of the shielding, the magnitude of the distance which should intervene between the operator and the material will be dictated by the nature and quantity of material handled and the maximal permissible daily dose of radiation which is considered compatible with safety. This quantity, which has been set at 0.1 roentgen equivalent man per day is presumed to be safe by roentgenological standards but there are some geneticists who are concerned lest even this small dose increase the mutation frequency of germinal tissue.

Out-and-out laboratory accidents are of course to be avoided and all precautions have to be taken to prevent contamination of laboratories as a result of spillage or breakage. More subtle is the hazard of volatile radioactive materials, such, let us say, as carbon dioxide containing carbon 14. Shielding and distance will no longer serve as a safeguard if such a gas escapes into the laboratory air. Monitoring devices are generally employed to inspect all likely sites of radioactive contamination from time to time, and exposed workers carry such monitoring devices about with them at all times.

Yet another hazard, perhaps not quite so grave, is the danger that, incident to radioactive contamination, the worker will arrive at an incorrect experimental conclusion. Since these radioactive materials will withstand almost astronomical dilution before all trace of them vanish, the cleansing of any surface which has been in contact with such materials becomes extremely difficult, and the danger is ever present that

radioactivity which has been ascribed to a sample of water may in fact due to an infinitesimal amount of contaminant adhering to the vessel from some previous use. It has even been argued that whole laboratories have been contaminated to such an extent as to render them completely unfit for further studies involving the measurement of radioactivity.

One of the most puzzling problems in regard to the use of radioactive isotopes is the question of the disposal of waste. In the course of any such study, inevitably there are residues and triflings, and if these contain radioactive isotopes of relatively long life, what to do with them becomes a major problem. The usual methods, for the disposal of wastes, incineration, burial, or discharge into the waterways or the ocean, have sufficed for the present, but none of these would appear to be a proper long-term solution to the problem. It may be that no entirely satisfactory solution to this problem will be found until rockets capable of delivering these wastes to interstellar space become available.

When I was invited to participate in this program, I was asked, among other things, to "look into the future" in regard to the usefulness of isotopes in medical research. Of the usefulness of isotopes thus far, I need say nothing, as the two succeeding speakers this evening will, by their experimental and clinical results, amply justify the existence of this tool. With the greater accessibility of both isotopes and instruments, it is becoming evident that increasing numbers of laboratories and hospitals are adding this tool to their armamentarium and the time is not far distant when the handling of isotopes will be as widely disseminated as is the operation of a Warburg apparatus. It must not be imagined, however, that isotopes are a substitute for brains and that all problems immediately resolve themselves when the aid of isotopes is invoked. In certain types of problems isotopes will prove extremely valuable. In other problems isotopes will continue to be unnecessary and valueless. As in the past, the success of a biochemical investigation will depend primarily upon the insight of the investigator and upon his skill in the handling of biological materials and in the classical operations of synthesis, isolation, purification, and analysis.

AN EVALUATION OF VACCINATION AGAINST EPIDEMIC INFLUENZA IN MAN*

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SINCE the initial discovery of human influenza virus in 1933 by Smith, Andrewes, and Laidlaw¹ many fundamental investigations on epidemic influenza have served to provide a sound scientific basis for the recent development of an at least partially successful method for active immunization against the natural disease in man.²

While these basic background studies cannot be reviewed in detail in the time available this evening, it would, nevertheless, seem desirable to mention some of the high points by way of introduction to the main subject, namely, an evaluation of vaccination against epidemic influenza in man. These background studies may conveniently be divided into those which were carried out from 1933 to 1942 and those which have been conducted from 1942 to date, concurrently with the attempt of the Commission on Influenza of the Army Epidemiological Board³ to determine whether a demonstrably successful and at the same time practical method of vaccination against influenza could be accomplished.

Following the initial demonstration by Smith, Andrewes, and Laidlaw¹ in 1933 that a filtrable virus in the throat washings of patients with influenza could be transmitted to ferrets and that the serum from recovered ferrets and convalescent humans would neutralize the infecting capacity of this virus, these important observations were promptly confirmed by Francis⁴ in 1934 by recovery of strains of the virus from cases of influenza in Puerto Rico and Philadelphia. During this same year both Andrewes, Laidlaw and Smith⁵ and Francis⁴ demonstrated that the strains of virus recovered from patients by inoculation of ferrets could be adapted to Swiss mice by repeated passage, thereby greatly facilitating further studies of the virus and laying the groundwork for the subsequent development in 1935 of an accurate neutralization test.^{6, 7, 8} By utilization of this test Francis⁷ then showed that the

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British W.S. strain, the Puerto Rican PR8 strain and the Philadelphia strain were immunologically similar, thus establishing the etiological identity of epidemics of influenza occurring in widely separated areas at this time.

Equally important was the demonstration in this same year by Francis and Magill¹¹ that in patients with influenza acute phage serum failed to neutralize the virus while early and six months' convalescent serum protected mice against infection, thus showing that humoral antibodies developed in humans, as well as in ferrets, in response to infection with the virus. This observation, confirmed in 1936 by Smorodintseff, Drobyshevskaya and Shishkina,¹² and subsequently by many others, made possible numerous important immunological studies and a method for proving diagnosis, much more widely applicable than the recovery of virus by inoculation of ferrets.

Three further important observations were reported in 1936. The first was by Smith, Andrewes, and Laidlaw¹³ that ferrets and mice could be infected only by way of the respiratory tract but not by subcutaneous or intraperitoneal inoculation. This fact was then utilized by Francis and Magill¹¹ to show that mice could be actively immunized against intranasal inoculation by means of subcutaneous or intraperitoneal injection of active mouse-lung or ferret-lung PR8 virus, thus establishing the principle that active resistance to experimental infection could be accomplished. The second observation was the successful cultivation of the virus in tissue culture medium consisting of minced chicken embryo in Tyrode's solution by Francis and Magill,¹⁴ and the third, of great importance for subsequent work, was the demonstration by Burnet¹⁵ that influenza virus could be adapted to grow on the chorioallantoic membrane of embryonated hens' eggs.

Further advances in 1936 were the development of a complement fixation test for determination of antibodies by Smith,¹⁶ a more rapid method than the neutralization test in mice; the demonstration by Magill and Francis¹⁷ that, though antigenically similar, nevertheless differences did exist among strains of virus from different sources; and observations of epidemiological import, by Francis and Magill,¹⁸ on serum antibody levels in normal individuals of different ages, which showed that 49.2 per cent had sufficient neutralizing antibodies to provide complete protection in mice, 29.4 per cent partial protection and only 21.3 per cent no protection. The studies on variations in antigenic

structure, subsequently confirmed and elaborated by Burnet,¹⁷ Magill and Francis,¹⁸ Francis and Magill,¹⁹ Smith and Andrewes,²⁰ Burnet and Lush,²¹ Horsfall and Lennette,²² Magill and Sugg,²³ and others, have become of obvious importance in the selection of strains for vaccines and in the interpretation of results obtained by vaccination.

In 1937 additional discoveries were made. The more important of these were, first, the report by Francis²⁴ of failure to recover virus or demonstrate a convalescent rise in antibodies to the PR8 strain in an epidemic in California in the early months of 1936, suggesting that this epidemic was due to a new and different virus, which four years later was proved to be the case; second, the studies of Francis and Magill^{25, 26} which showed that on occasion, though not readily, the virus of influenza might be recovered by direct inoculation of human throat washings in mice, tissue cultures and on the chorioallantoic membrane of embryonated eggs; and third the experiments of Smorodintseff *et al.*²⁷ in which it was shown that normal human subjects with little circulating antibody were readily infected experimentally while subjects with relatively high antibody titers were resistant, thus demonstrating a relationship between humoral antibody levels and susceptibility or immunity. In harmony with these experimental results were the simultaneous observations of Hoyle and Fairbrother²⁸ comparing antibody titers in a population group before and after an epidemic, those of Francis, Magill, Rickard, and Beck²⁹ on 120 cases in the 1936-37 epidemic comparing acute phase titers with convalescent phase titers, which showed approximately a tenfold rise, and those of Rickard, Horsfall, Hirst and Lennette³⁰ in the 1940-41 epidemic, in all of which it was shown that the level of antibodies was an important factor in susceptibility or resistance. Included in the report of Francis and his collaborators²⁹ were observations bearing on the important question of duration of immunity. Two and a half to five months following recovery antibody titers had fallen on the average about 50 per cent below the early convalescent level. There was, however, considerable individual variation.

The preceding year, 1936, saw the initiation of studies on vaccination of man against influenza. Among these may be mentioned those of Chenoweth, Waltz, Stokes and Gladen³¹ with human and swine viruses; of Francis and Magill³² and Stokes and his collaborators^{33, 34} with an active culture virus vaccine in 1937; of Stuart-Harris, Andrewes

and Smith^{35, 36} and of Taylor and Dreguss³⁷ with a formalin-inactivated mouse-lung vaccine from 1938 to 1940; of Siegel and Muckenfuss³⁸ in 1940 with active virus; and those of Horsfall, Lennette, Rickard and Hirst,³⁹ of Dalldorf, Whitney and Ruskin,⁴⁰ and of Eaton and his collaborators⁴¹ with a complex influenza-canine distemper vaccine⁴² in 1941. Suffice it to say that while all of these vaccines, none of which was significantly concentrated, stimulated some rise in antibodies in the vaccinated individuals, there was no acceptable evidence forthcoming that they induced a sufficient degree of resistance to natural infection to warrant their use on a wide scale.

In the meantime, experiments by Francis,¹² reported in 1939, showed that, within certain limits, a direct proportional relationship existed between the concentration of virus used for immunization of mice and the degree of active immunity to intranasal infection induced, a result which of course suggested that a more concentrated vaccine than those being tried would be necessary to produce an effective immunity in man. As will appear later in the discussion, this suggestion has been found to be valid.

In November, 1940, Horsfall⁴³ published a review on the status of knowledge concerning influenza at that time. From this review I have culled certain items which it seems worthwhile at this point either to quote or to paraphrase since it may serve to emphasize the rapid progress which has been made since that time.

The first item relates to the etiology of influenza. Calling attention to the failure to recover a virus or demonstrate a rise in antibodies to the W.S. or PR8 strains of virus in certain epidemics in California in 1936, in England in 1939, and North Carolina in 1940, Horsfall endorsed the joint proposal from the International Health Division of the Rockefeller Foundation and the National Institute for Medical Research, Hampstead, London⁴⁴ that the specific disease caused by virus immunologically like the W.S. and PR8 strains be designated influenza A and that the terms influenza B, C, etc., be reserved for influenza caused by as yet unidentified and still hypothetical viruses immunologically distinct from A, if and when discovered.

The second item concerns the time required to identify an epidemic by recovery of the virus. I quote, "The recovery and identification of influenza A virus from a given throat washing require considerable time and even under the most favorable circumstances cannot be accom-

plished in less than three weeks."

Horsfall goes on to say that though Francis and Magill^{25, 26} had succeeded in establishing the virus directly in mice, tissue culture and on the chorioallantoic membrane of the developing chick embryo without preliminary ferret passage, this had been successful in only a small proportion of cases, and that it should be emphasized that no rapid or simple method had yet been devised for the demonstration of influenza A virus in a given throat washing.

The third item concerns the time required to identify an epidemic by serological means. Pointing out that a significant antibody rise diagnostic of influenza A can be considered demonstrated only when the titer of the convalescent serum is four or more times higher than the titer of the acute phase serum and that antibodies reach maximum levels only within ten to fourteen days after the onset of influenza, Horsfall states, "Given ideal conditions, it is possible to obtain evidence of an increase in specific antibodies by means of the complement fixation test in from ten days to two weeks after the beginning of an epidemic. With the neutralization test a similar result can be achieved only within three weeks of the onset because of the additional time required for observation of the test mice."

And finally with respect to vaccination, with either active tissue-culture vaccine or inactivated mouse-lung vaccine, Horsfall concluded that there was "no convincing evidence . . . that either vaccine was effective in preventing the occurrence of the disease."

Hardly had this review by Horsfall appeared in print when Francis⁴⁶ reported the recovery and identification of a new type of virus obtained from patients in what appeared clinically to be an epidemic of influenza at Irvington House, Irvington on Hudson, in February and March, 1940. This virus, initially recovered by ferret inoculation, was adapted to mice by serial passage and by the 40th passage had become sufficiently virulent to kill regularly in a 1:1000 dilution. This strain of virus, called the Lee strain, was then shown by appropriate neutralization tests to be immunologically distinct from influenza A virus. It was further shown by the use of convalescent sera preserved from the previously unidentified February, 1936, epidemic in California that this epidemic was caused by a virus immunologically like the Lee strain. In accordance with the classification proposed by Horsfall *et al.*⁴⁵ the new strain was designated influenza B virus.

Almost simultaneously and quite independently Magill⁴⁷ reported the recovery of a new virus which was subsequently identified with the B virus by Magill.⁴⁸ Similarly by retrospective serological tests, Lennette, Rickard, Hirst and Horsfall⁴⁹ reported that epidemics in North Carolina and the West Indies in the Spring and Summer of 1940, respectively, were influenza B; Eaton and Beck⁵⁰ reported that cases in California in early 1940 were influenza B; and Nigg, Eklund, Wilson, and Crowley⁵¹ that cases in Minnesota in May 1939 were due to the B virus. Thus influenza B was established as an etiologically distinct type of influenza, though clinically similar to influenza A.

The next new and highly important discovery was made by Hirst⁵² in 1941 when he noted in the process of harvesting chicken embryo cultures that the red cells coming from ruptured blood vessels of chick embryos infected with influenza virus agglutinated macroscopically in the allantoic fluid within 15 to 30 seconds. Taking advantage of this observation, Hirst⁵³ then devised the hemagglutinin test for the quantitative determination of the amount of virus present in a fluid and the hemagglutinin-inhibition test for the quantitative determination of antibodies and the prompt differentiation of influenza A and B viruses. Hirst⁵³ further showed that the inhibition test for titrating antibodies correlated well with the neutralizing capacity of serums and also that the red cells under proper conditions not only adsorbed practically all the virus but that following adsorption elution took place, releasing nearly all the virus. These observations of Hirst may fairly be said to have revolutionized technics employed in the study of influenza and to have provided means for rapid identification of virus following the onset of an epidemic, for the extension by a readily performed and rapid method of studies on antibody content of serum, and one method for the concentration and standardization of vaccine.

Meanwhile, further advance had been made in the direct isolation of human influenza virus in chick embryos. In 1940 Burnet⁵⁴ reported direct isolation of seven strains by inoculation of throat washings into the amniotic sac. In 1942 Hirst⁵⁵ obtained twenty-eight positive results out of fifty-four filtrates of known positive throat washings which had been stored for fourteen to eighteen months at -76°C. In the November-December, 1943, epidemic of influenza A, Rickard, Thigpen, and Crowley⁵⁶ successfully recovered the virus by direct intra-allantoic inoculation of unfiltered washings in nine of twenty trials, four in the

first egg passage, and identified the epidemic as influenza A in forty-eight hours after the onset of the first case. Finally, in 1945, in a comparative study of various technics, Hirst⁵⁷ found that the inoculation of the amniotic sac with unfiltered washings to which 125 units of penicillin per cc. had been added was the most sensitive method, being successful in thirty-three out of forty-five trials.

The importance of the foregoing technics for the rapid recovery and identification of influenza virus, if vaccination is not undertaken until the appearance of a presumptive epidemic, is self evident, for as will appear later, immunity cannot be established in less than a week after vaccination.

With the foregoing background in mind let us now turn to a consideration of the development of the more effective vaccination against influenza which has taken place during the last five years, in an effort to evaluate the present situation and to point out some of the problems requiring further study for their solution.

Although Horsfall and his collaborators⁵⁸ had apparently obtained some success by vaccination with their complex chick embryo-canine distemper vaccine in 1940-41, with a decrease of approximately 50 per cent in the incidence of the disease among the vaccinated groups, the results were not consistent in all groups. In reviewing these results in a paper presented in April 1941, Horsfall⁵⁸ states, "Obviously these results do not indicate that a satisfactory and trustworthy immunizing agent against influenza A has been found. On the other hand, the reduction in incidence observed is not negligible and suggests that at least a step, however small, has been made in the direction of the eventual control of this disease. Furthermore, the results obtained tend to confirm the available evidence concerning the relationship between high antibody levels and relative immunity to influenza A and therefore may serve to point the way toward more effective prophylaxis. It seems possible that should a vaccine of considerably greater potency become available and should this improved vaccine increase specific antibodies to even higher levels, somewhat more striking reductions in the incidence of influenza A might be expected to result from its administration. Although these are intriguing problems for the future, it should be emphasized again that influenza A is merely one etiological variety of influenza. Until such time as those other unknown causes of the disease are discovered, it will hardly be possible to develop satisfactory

prophylactic measures against epidemics of influenza as such."

The next step, then, was an effort to develop a more potent vaccine by concentration of the virus and this was undertaken by a number of investigators. In 1942, Hirst, Rickard, Whitman, and Horsfall⁵⁹ in a comparative study of eleven different preparations of vaccine, ranging in strength from 36,200 to 214,000,000 50 per cent mouse mortality doses of influenza A virus per dose of vaccine and from 1000 to 1,000,000 50 per cent mouse mortality doses of influenza B virus per dose of vaccine, showed clearly that the strongest vaccines concentrated by high speed centrifugation were much superior to the weaker vaccines in stimulating antibody production and, in fact, induced a response quite comparable to that found in early convalescence from the natural disease. Subsequently Hirst, Rickard and Whitman⁶⁰ and Hare, McClelland and Morgan⁶¹ reported independently that when infected allantoic fluid is frozen and then permitted to thaw, concentrated virus may be obtained by collection of the precipitate which forms. The mean antibody level two weeks after vaccination with this concentrate was as high as that which followed vaccination by similar amounts of virus concentrated by centrifugation.

Likewise in 1942 Francis and Salk,⁶² taking advantage of Hirst's observation⁵³ on the adsorption on and elution of virus from chicken red cells, devised a simplified procedure for the concentration and purification of influenza virus and prepared an approximately ten times concentrated, mixed vaccine containing the PR8 and Weiss strains of A virus and the Lee strain of B virus. This vaccine also was shown to be antigenically more potent in actively immunizing mice and in stimulating higher antibody titers in humans than the unconcentrated vaccines previously tried. The main practical advantages of the eluate vaccine were considered to be that it could be maintained in fluid state at 4°C with unchanged potency for eighteen months and that it did not have to be rehydrated at time of injection. The major portion, though not all, of the inert chicken protein was eliminated.

With these more concentrated vaccines available and in the expectation that an influenza epidemic might occur during the winter of 1942-43, the Army Epidemiological Board's Commission on Influenza, under the direction of Dr. Francis, undertook the vaccination of groups of individuals with appropriate controls in various state institutions both with the frozen and thawed precipitate vaccine and the eluate

vaccine. Unfortunately, the prompt determination of the effectiveness of these vaccines in preventing the natural disease was frustrated by the failure of the expected epidemic to occur.

In the interval before the next epidemic, however, it was possible to conduct studies on the distribution of antibody titers at two weeks, four months and one year after vaccination.⁶³ These observations, which presumably have some bearing on the duration of immunity following vaccination, if expressed in the percentage of individuals having titers above certain levels, showed that for type A virus antibody titers of 256 or more were found in 15 per cent before vaccination, 83 per cent two weeks after vaccination, 69 per cent four months later and 66 per cent after one year, while for type B virus the corresponding figures were 6 per cent, 82 per cent, 70 per cent and 57 per cent, respectively. Francis,⁶⁴ Salk⁶⁵ and their collaborators were further able to show that individuals with antibody titers of 256 or more were relatively insusceptible to experimentally induced influenza A and B, when compared with those with titers of less than 256.

Even more important was their demonstration^{66, 67} in a controlled study at the Ypsilanti State Hospital in Michigan that the vaccine had a significant protective effect against experimentally induced influenza A and B. In summarizing the results in the case of influenza A, the authors record⁶⁶ that clinical reaction with temperatures of 100°F. or more occurred in 50 per cent of the controls, 32 per cent of those vaccinated four and one-half months before, 14 per cent of those two weeks before, and 18 per cent of those vaccinated both four and one-half months and two weeks before challenge. None in the recently vaccinated groups had temperatures over 100.8°F. while 25 per cent of the controls and 11 per cent of those vaccinated four and one-half months before had fever of 101°F. or higher. Febrile reactions following exposure to virus occurred in 49 per cent of individuals having pre-infection antibody titers of 128 or less and in only 14 per cent of those having titers of 256 or more. Comparable results were obtained⁶⁷ with influenza B, although in this case the immunizing effect at four and one-half months was somewhat better maintained.

With this data at hand it was possible to set up in 1943 a well-controlled experiment in Army Student Training Program Units in nine universities throughout the country.^{68, 69} The participants in this investigation were Rickard, Thigpen and Crowley,⁷⁰ University of

Minnesota; Hale and McKee,⁷¹ University of Iowa; Eaton and Meiklejohn,⁷² University of California; Hirst, Plummer and Friedewald,⁷³ Princeton and Rutgers Universities and the College of the City of New York; Salk, Menke and Francis,⁷⁴ University of Michigan; and Magill, Plummer, Smillie and Sugg,⁷⁵ Cornell University and five medical and dental colleges of New York City. *In toto* between October 19 and December 4, 6,263 students were vaccinated subcutaneously with 1 cc. of a formalinized, allantoic fluid eluate, Type A and B, 10^x concentrated vaccine, made up of the PR8 and Weiss A strains and the Lee B strain of virus; 6,211 comparable, alternate controls were injected at the same time with comparable material, excluding the virus.

Fortunately for the experiment, epidemics of influenza A developed in all these institutions in late November or early December. In the whole group, the incidence of influenza during the epidemic was 2.22 per cent in the vaccinated as against 7.11 per cent in the controls or a reduction in incidence of approximately 70 per cent. Expressed in another way 76.2 per cent of all cases occurred in the controls, 23.8 per cent in the vaccinated. Furthermore, the protective effect was comparable in all institutions except the University of California where the time elapsing between vaccination and the outbreak was considerably longer than in the others, approximately six to twelve weeks after vaccination from onset to termination of the epidemic. Whether this or some other factor was responsible for the less striking results at the University of California is uncertain. In the study at C. C. N. Y., because vaccination and onset of the epidemic were simultaneous, an opportunity occurred to show that resistance developed about eight days after vaccination.

It now remained to determine how effective this vaccine might be against an epidemic of influenza B and the opportunity occurred during the fall of 1945 at the University of Michigan, at Yale and in a small group at the Medical College of Alabama. Six hundred Army students had been vaccinated at Michigan on October 16, 1945, 550 at Yale, the majority on October 19 and a few early in November, and thirty at Alabama on December 4. For comparison there were 1100 unvaccinated Navy students at Michigan, 1050 at Yale, and ninety-five Navy and civilian students at Alabama. The results at Michigan, reported by Francis, Salk and Brace,⁷⁶ showed an incidence of influenza B among the vaccinated of 1.15 per cent, in the unvaccinated an incidence of

9.91 per cent. The results at Yale, reported by Hirst, Vilches, Rogers and Robbins,⁷⁷ were even more striking. There were 132 Navy cases or an attack rate of 12.5 per cent, only three Army cases or an attack rate of 0.5 per cent. At Alabama Friedman⁷⁸ reported two cases in the vaccinated group, 18 in the unvaccinated.

An analysis⁷⁹ of the data for the Army and Navy in the United States during this period would appear to be in harmony with the foregoing observations concerning the protective effect of vaccination against influenza B, the rate for common respiratory disease including influenza being in the Army, which had been vaccinated, approximately one half that in the Navy, which had not been vaccinated, a difference which did not occur during the influenza A epidemic in December 1943, when neither Army nor Navy personnel were vaccinated.

A similar satisfactory result has been reported by Norwood and Sachs⁸⁰ in a large industrial group. Among 360 vaccinated employees the incidence of influenza B was 1.94 per cent, among 4,280 unvaccinated employees 8.23 per cent, absenteeism being 4.4 x greater in the unvaccinated than in the vaccinated.

In summary, then, it would appear that in two adequately controlled experiments a considerable degree of success was attained in vaccination against the influenza A epidemic of November-December 1943 and the influenza B epidemic during the late Fall of 1945 under the following conditions: 1) when a potent formalinized and concentrated vaccine, in a single dose of 1.0 cc. subcutaneously and capable of stimulating an antibody response comparable to that which develops early in convalescence, was used; 2) when the antigenic structure of the strains of virus used in the vaccine was closely similar to that of the strains causing the epidemics; and 3) when vaccination had been carried out within 1 to 6 weeks prior to the onset of the epidemic.

Let us now review briefly the experience of 1946-47. On the basis of accumulated epidemiological experience,⁸¹ which has suggested that influenza A epidemics occur every two to three years with sharper epidemics after the longer interval and that influenza B epidemics occur every four to six years, it was expected that an epidemic of influenza A might occur in the late Fall or early Winter of 1946-47. Consequently a number of large scale vaccination programs were instituted in several educational institutions and industrial companies.^{82,83}

At the University of Michigan⁸⁴ 10,328 students were vaccinated between October 22 and November 2, 1946, with 7,615 unvaccinated students serving as controls. No epidemic appeared, however, until early March 1947, four months after vaccination. Between then and April 4 the incidence of acute respiratory disease was approximately the same in the vaccinated and unvaccinated groups, 7.19 per cent and 8.09 per cent, respectively. Subsequent studies by Francis, Salk and Quilligan⁸⁴ have shown that the virus concerned in the epidemic was apparently influenza A but that a sharp antigenic deviation from the standard PR8 strain was demonstrable. In the acute stage of the disease the mean antibody titer against PR8 virus was seventy-six in the unvaccinated, 499 in the vaccinated. In sharp contrast there was no difference in the low titers of vaccinated and unvaccinated against the 1947 epidemic strain. Ferrets inoculated with the new strain developed high antibody titers for the recently isolated 1947 strain but less response for the PR8 and Weiss strains of influenza A, while ferrets inoculated with the PR8 and Weiss strains exhibited high titers for these strains but little or no antibodies for the 1947 strains. The authors conclude that the failure of vaccination during the 1947 spring epidemic of influenza appeared to be due to lack of sufficient antigenic crossing between the strains in the vaccine and the prevalent epidemic strain.

At Yale⁸⁵ approximately 4,000 students were vaccinated during the fall of 1946. As at Michigan, there was no apparent difference in the incidence of influenza in the vaccinated and unvaccinated students when a mild epidemic of influenza appeared in late February and March, 1947, three to four months after vaccination.

Smadel⁸⁶ has reported a similar unsatisfactory result in the Army. Late in January 1947 outbreaks of influenza occurred at Fairfield-Suisun Army Air Base, California, Lowry Field, Colorado and Fort Monmouth, New Jersey. By serological tests these were identified as type A and on February 8 influenza vaccine was given to all military personnel. Subsequent epidemics occurred in a number of Army installations without any satisfactory evidence to show whether vaccination reduced the incidence or not. Strains recovered from patients at Lowry Field, Scott Field and Fort Monmouth were found to be antigenically closely related to each other but only distantly related to the standard PR8 and Weiss strains contained in the vaccine. Furthermore, the vaccine used did not elicit a good antibody response against the 1947 strain though

it did against the PR8 virus.

It has become quite obvious from the foregoing discussion that, despite the not inconsiderable success which has attended the work of the last five years on vaccination against influenza, many important, practical questions still require study and solution before a universally effective vaccine is at hand which will meet all the requirements of this difficult and complex problem of preventive medicine. To enter into a hypothetical discussion of these questions is probably not too profitable but nevertheless rather tempting. Suffice it, then, in bringing this discussion to a close, to ask some of these questions and answer them tentatively so far as possible on the basis of existing knowledge.

First, what is the best type of vaccine? At least four problems are involved in this question—antigenic effectiveness, toxicity, allergenic properties, and economic production on a mass scale. With respect to antigenic effectiveness, it would appear to be well established that formalin-inactivated and concentrated vaccine, containing approximately 0.2 to 0.25 mg. of virus material per cc., and irrespective of the method of concentration, is adequate to stimulate a satisfactory antibody response in approximately 85 per cent of individuals vaccinated, if a titer of 256 or greater be considered satisfactory. Various methods of concentration have been studied, including adsorption on calcium phosphate by Salk,^{87,88} precipitation with protamine by Chambers and Henle,⁸⁹ freezing and thawing by Hirst, Rickard and Whitman⁶⁰ and Hare, McClelland and Morgan,⁶¹ adsorption and elution from chicken red cells by Francis and Salk,⁶² high speed differential centrifugation by Stanley⁶⁰ and by Taylor *et al.*,⁹¹ and methanol-precipitation followed by Sharples centrifugation by Cox, van der Sheer, Aiston and Bohnel.⁹² Although the red cell eluate vaccine is the only one that has as yet been demonstrated by extensive, well controlled field trials to be prophylactically effective against naturally occurring epidemics, there is no reason to suppose, as pointed out by Salk,⁹³ that vaccines prepared by other methods of concentration would not be equally effective, provided they contain an equivalent amount of antigenically active virus. Though it is true, as emphasized by Stanley,⁶⁰ that a much more concentrated and equally antigenic vaccine can be prepared by high speed differential centrifugation than by the elution method, this is of little practical significance in so far as increasing the amount of virus per cc. of vaccine is concerned, since more virus per dose than

that in the eluate vaccine would make the vaccine too toxic for practical use, unless some method can be devised for detoxifying the virus without destroying its antigenicity. A somewhat different point of view, however, has been expressed by McLean, Beard and Beard,⁹⁴ based on their studies on the immunization of swine against swine influenza. Feeling that little further improvement is to be expected by increasing the dose, repeating the dose or by further concentration and purification of the virus from which the vaccine is made, they suggest, instead, that it would seem advantageous to direct more attention to the utilization of an active, attenuated virus, as described by Burnet and Foley.⁹⁵

Concerning the problem of toxicity, which appears to depend upon the concentration of virus in the vaccine,⁹³ the reports in the literature appear to be quite conflicting with respect to the frequency of local and systemic reactions. Without attempting to analyze them in detail, it may be stated, I believe, that with the eluate vaccine the character and frequency of the reactions are fairly comparable to those seen with typhoid vaccine, annoying but not serious; that with protamine-precipitation vaccine the reactions are of similar character but reportedly less frequent;^{82,83} and that neither kind causes absenteeism of consequence in industrial groups,^{80,82,83} when compared with the absenteeism caused by epidemic influenza itself. It is to be hoped that future studies on methods of detoxification will lead to a reduction in the frequency and severity of toxic reactions, but in the meantime they would hardly seem sufficient to act as a deterrent to the use of the vaccines now available.

With respect to allergic reactions, which, as Ratner and Untracht⁹⁶ have shown, are related largely if not entirely to egg white protein in the vaccine, it would appear from wide experience that there need be little concern in adults, provided the essential precaution is taken to exclude from vaccination those known to be sensitive to eggs. In children, on the other hand, Ratner and Untracht⁹⁶ report on the basis of a careful study, that 1 in 200 may be sufficiently sensitive to require caution. They advocate an intradermal test with 0.02 cc. of vaccine, withholding vaccination in all cases of systemic reaction and giving the vaccine in three to six divided doses at one to three day intervals in cases showing only local reaction to the skin test. That it would be advantageous to reduce the amount of egg protein in the vaccine to a

minimal amount seems self-evident. From this point of view it would appear that vaccine prepared by differential high speed centrifugation would be preferable but even in the most highly purified preparations of PR8 and Lee viruses obtained from infectious allantoic fluid Knight⁹⁷ has shown that there is at least about 20 and 30 per cent, respectively, of an antigenic component characteristic of the sedimentable protein of normal allantoic fluid.

Concerning the problem of economical mass production it is perhaps, as yet, impossible to make any categorical statement, but a combination of precipitation followed by high speed centrifugation⁹² would appear to be the most promising.

Secondly, what is the best method of vaccination with respect to dose and method of injection. It would now appear established, through the controlled studies of the Commission on Influenza, subsequently confirmed by others, that a single dose of 1.0 cc. of the eluate vaccine given subcutaneously is adequate to produce a highly satisfactory antibody response and a high grade of resistance to infection.^{63, 68} This dosage, however, is attended by more frequent toxic reactions than is desirable. Efforts to solve this problem are being made. Van Gelder, Greenspan and Dufresne,⁹⁸ in a comparative study in 1952 Navy personnel, have reported that a single dose of 0.1 cc. of vaccine given intracutaneously produced a higher rise in antibody titer than 1.0 cc. subcutaneously against both virus A and virus B, but this result as yet lacks confirmation and the degree of immunity against an actual epidemic provided by this method of immunization has not been determined. Until this is done, it remains an experimental procedure and cannot be advocated for general adoption.

More recently Salk⁹⁹ has reported that a single dose of vaccine given subcutaneously in amounts sufficient to be attended by a toxic reaction did not necessarily produce a higher antibody titer than somewhat smaller doses unattended by uncomfortable reactions. He has advocated for the present the largest possible dose of virus that can be given without systemic reaction. For adults this would be about one-fourth to one-half of the dose now being used. Here again these preliminary results must run the gamut of confirmation and a controlled field experiment before they can be adopted with confidence.

Thirdly, what is the actual effective duration of immunity following vaccination, when and how often should vaccination be done? Observa-

tions by Hirst, Rickard and Friedewald¹⁰⁰ on 2,945 individuals vaccinated 12-14 months prior to an outbreak of influenza A, when compared with a comparable control group of 4,451 persons, showed an attack rate of 3.6 in the vaccinated as against 5.5 in the controls, or a reduction of 35 per cent. Similarly Salk *et al.*⁶³ have reported that in a group of 2,086 persons in Ypsilanti State Hospital, of whom 1,035 were vaccinated in December, 1942, and 1,051 served as alternate controls, the attack rates during an influenza A epidemic one year later were significantly lower in the vaccinated wards than in unvaccinated wards—in the female wards 3.4 per cent against 14.5 per cent, in the male wards 0.9 per cent against 9.7 per cent. It is further significant that, in the vaccinated wards of the hospital where only half of the patients had been vaccinated, this in itself seemed sufficient to check the spread of the disease to the unvaccinated controls in these wards. From the data available, then, it would appear that a considerable degree of immunity persists in a population group one year after vaccination. The tentative conclusion is that annual vaccination would seem the most desirable and practical procedure at present.

With respect to the most appropriate time of the year for vaccination, I believe it may be stated with considerable confidence that vaccination should be done prior to the appearance of an epidemic if the best results are to be obtained, for two reasons. The first is that it requires at least a week to establish immunity, the second that epidemics ordinarily spread so rapidly that it is impractical to undertake mass vaccination with the expectation that it can be carried through and immunity established before the epidemic has reached its peak in any given community. If this be accepted, October would appear to be the most appropriate time for vaccination since most epidemics occur in the late Fall or Winter months. The question naturally arises whether because of the periodicity of influenza vaccination should be practiced only in those years when an epidemic is expected. In this connection Francis¹⁰¹ has said, "One of the chief obstacles to proper evaluation is the lack of cooperation on the part of the disease itself, in not presenting itself in the desired spot at the desired time." I would state it another way by saying that the chief obstacle is lack of knowledge which would enable us to predict with mathematical certainty when the next epidemic is going to occur.

Fourthly, what strains of virus should be used in the vaccine? Clearly

both A and B types of virus should be included, but what strains of each type? As pointed out above it has been well established by many investigators^{102, 103} that within each type a considerable degree of antigenic deviation may occur with the result that the strains included in the vaccine available at any given time may not be adequately protective for the strain to be encountered in the next epidemic. This difficulty was conspicuously illustrated by the unsatisfactory results obtained in the epidemic of last winter. Whether master strains can be found of sufficiently broad antigenic constitution to cover all strains within a type is a problem of continued research. In the meantime it would seem desirable to include with PR8 and Lee viruses, strains from the most recent epidemic and this is now being done by the inclusion of the FM1 strain of influenza A from the 1947 epidemic.⁸⁶

Finally, concerning these and other problems awaiting solution, it is to be expected that final answers will be obtained only through continued research in the laboratory and the field. Certainly, it would not appear outside the realms of possibility that the resistance of the population as a whole may be raised and maintained at a level sufficient to forestall and prevent another disastrous pandemic.

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SECTION ON MICROBIOLOGY

FEBRUARY 18, 1948

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H. Sherwood Lawrence

Third Medical Division, Bellevue Hospital

III. DISCUSSION

Gregory Shwartzman, Chairman

Harry Most, Secretary

The Preparation and Properties of Purified Toxins and Toxoids

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Chemical investigations on bacterial toxins and toxoids are of practical and theoretical significance not only in the field of immuno-chemistry but also in the related preclinical and clinical sciences. The ultimate aim of such studies is to determine the nature, the character, the relationship between the biological and chemical properties, and the mode of action of toxins and toxoids.

The proper approach to these problems should concern first the determination of the physical, chemical and immunological properties of toxins and toxoids. In order to accomplish this, isolation of these substances in pure form is necessary. It is the purpose of this paper to discuss recent efforts to purify and characterize tetanous toxin and toxoid and diphtherial toxoid.

Both Eaton and Pappenheimer have prepared diphtherial toxin in a state of high purity. Groups of Army and Navy personnel at Camp Detrick have crystallized botulinal toxin (Type A). These investigators employed the classical methods of protein purification which involve the use of neutral salt precipitation, acid precipitation and adsorption. These procedures are largely based on the work of Denis and others which was carried out approximately a century ago, long before the chemical nature of proteins was understood. Although such empirical methods have yielded satisfactory preparations, it appears that these procedures leave much to be desired and that the problem of purifying toxins and toxoids should be solved by the employment of

precise methods which conform to the disciplines of physical chemistry.

Using the basic principles developed by Cohn and his associates for the fractionation of blood plasma in ethanol-water mixtures at low salt concentrations and low temperatures, the author and his colleagues have prepared crystalline tetanal toxin and highly purified staphylococcal and pertussal toxins. Pure diphtherial and tetanal toxoids have also been prepared. The methods employed involve the use of methanol-water mixtures under precisely controlled conditions of pH, ionic strength and temperature and have been reported in detail elsewhere.

Crystalline tetanal toxin has been characterized as a heat labile protein with an isoelectric point of 5.1 ± 0.1 . The toxin has an electrophoretic mobility of 2.8×10^{-5} in veronal buffer of 0.1 ionic strength at pH 8.6 and has a sedimentation constant of 4.5 Svedberg units. Freshly prepared toxin has substantially constant solubility. The crystalline toxin gives the usual protein reactions, and contains 1 per cent sulphur and traces of phosphorus. It does not contain carbohydrate. The crystalline protein does not precipitate anti-*Clostridium tetani* rabbit serum. Four times recrystallized tetanal toxin contains between 3400 and 3600 flocculating units and about 6.6×10^7 mouse minimal lethal doses per mg. of N. Crystalline tetanal toxin spontaneously converts to a flocculating atoxic dimer upon standing at 0° C. This change is accompanied by the appearance of another molecular species judged both by constant solubility test and ultracentrifugal analysis. The flocculating atoxic dimer has a sedimentation constant of 7 Svedberg units.

Pure diphtherial toxoid has been separated as a heat labile protein with an electrophoretic mobility of 8.1×10^{-5} in veronal buffer of 0.1 ionic strength at pH 8.6 and with a sedimentation constant of 4.6 Sved-

berg units. Its isoelectric point is 4.7 ± 0.1 . The preparation has constant solubility and satisfies the existing criteria for a pure protein. It does not contain sulphur, phosphorus, carbohydrate or iron. The purified diphtherial toxoid does not precipitate anti-*Corynebacterium diphtheriae* rabbit serum. The final product contains between 2000 and 2200 flocculating units per mg. of N.

Purified diphtherial and tetanal toxoids obtained by the low temperature methanol method are now commercially available. They possess a number of practical advantages which may be summarized as follows. These toxoids which are more than 200 times purer than crude preparations generally do not elicit side-reactions when administered to children and adults. In general, it is no longer necessary to carry out reactor tests, and "booster" doses may be given without hesitation. The immunity obtained with these products is durable and of high order. The immunizing power of toxoids is potentiated by alum precipitation but unfortunately alum occasionally produces local irritation at the site of injection. Since the new preparations contain fewer solids, they can be precipitated with one-tenth the amount of alum required for crude toxoids. Side reactions to alum are therefore minimized. The addition of glycine permits sterilization by filtration and allows storage of these preparations for long periods of time under extreme temperature conditions without deterioration. Finally, since these toxoids are pure and stable they can serve as primary standards for the biological evaluation of products of equal or lesser purity.

The above mentioned advantages should lead to an increased use of toxoids for the prevention of diphtheria and tetanus. It should also lead to an intensified effort to purify by similar methods other toxins, toxoids and bacterial antigens.

*The Iron Enzymes of *C. Diphtheriae*
and Their Possible Relation to Diphtheria Toxin**

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Studies on toxin production by *C. diphtheriae* have suggested that diphtheria toxin may be concerned in some way with the respiratory mechanism of the bacterial cell. Thus toxin is only produced under strictly aerobic conditions. In 1931, Coulter and Stone¹ showed that a free porphyrin is produced in culture filtrates in concentrations paralleling toxin production. This porphyrin has recently been identified as coproporphyrin III (Gray and Holt²). Finally both toxin and porphyrin are only produced in high yield when the iron concentration of the culture medium is very low.³ In the case of the Toronto variant of the PW8 strain, for every 4 atoms of iron added over and above the optimum, 4 molecules of porphyrin and one of toxin fail to appear in the culture filtrate. Bacterial growth at optimal iron concentration for toxin production is about 80 per cent that obtained with excess iron. However, cells harvested from media containing an excess of iron contain 5-6 times as much iron as cells grown under conditions most favorable for toxin production. Cell suspensions of high iron content show a 2-banded hemochromogen type spectrum when treated with sodium hydrosulfite and dilute alkali. These facts suggest that diphtheria toxin may be the protein moiety (or closely related precursor) of a respiratory enzyme. From the quantitative relationships between iron, porphyrin and toxin, the postulated enzyme should be the major respiratory pigment of diphtherial cells of high iron content.

The major hemin-containing pigment of *C. diphtheriae* is spectroscopically related

to cytochrome *b* as was first noted by Fujita and Kodama.⁴ It has been shown that cytochrome *b* is the limiting factor in the oxidation of succinate to fumarate by extracts of the diphtheria bacillus. The system which oxidizes succinate in these extracts is characterized by its insensitivity to cyanide, naphthoquinone SN5949 (Ball *et al.*⁵) and carbon monoxide, compounds which inhibit the succinoxidase system in extracts from mammalian tissues. The differences between the diphtherial succinoxidase system and that of beef heart (Keilin and Hartree⁶), have been studied and can be explained by the presence in the bacteria of large amounts of cytochrome *b* relative to the other cytochrome components, cytochrome *c* and cytochrome oxidase, known to participate in the succinoxidase system.

These findings suggest the possibility that diphtheria toxin may interfere with the normal function of cytochrome *b* in the tissues of susceptible animals, possibly by blocking its synthesis.

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The Present Status of Immunization Against Diphtheria

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It is a pleasure to acknowledge the courtesy of the invitation to address the Academy and an honour to pay tribute to two of your illustrious members who have played such a prominent part in the control of diphtheria, namely William Halleck Park, and Béla Schick who is in the audience tonight. Time does not permit more than a very respectful nod to the past. It is to Ramon of the Pasteur Institute we owe the introduction of formol toxoid, a safe, easily standardized, inexpensive and very effective antigen for active immunization against diphtheria. The study of the effectiveness of toxoid in Toronto school children made at a time of high prevalence of diphtheria showed that three doses given at three weeks' interval resulted in a 90 per cent reduction as compared with the rate of their uninoculated school mates. That study initiated in 1927 had to be abandoned for the sole reason that the morbidity rate from diphtheria dropped to such a low figure and there maintained up to the present, as to make any comparison between the inoculated and non-inoculated meaningless.

Diphtheria has not been controlled by isolation and quarantine. Essentially, the control rests upon the simple principle of producing the most effective degree of active immunity in the greatest number of persons as early in life as possible and maintaining that immunity indefinitely. Administratively this looks like, and perhaps is, a formidable task. It has long been known that the response to toxoid and the loss of antitoxin are both subject to very wide individual variation. Both of these factors may be countered by giving the "dose de rappel" of Ramon, or more commonly designated recall or booster dose, in suitable quantity and at appropriate intervals. The basic principle of the secondary stimulus or recall dose has long been known. In 1898

Dean at Oxford showed the prompt and high rise in antitoxin in response to a secondary stimulus in a horse previously hyperimmunized and rested some years. Rufus Cole clearly enunciated that principle in 1904. He showed that a secondary stimulus in itself too small to elicit a detectable antibody response caused a rapid rise in agglutinins in an animal previously immunized and whose antibody titre had fallen to zero. More important perhaps than any other single factor in the control of diphtheria is the intelligent use of the recall dose.

There is a close analogy between active immunization against the diseases tetanus and diphtheria. Their respective toxoids readily call forth an antitoxic immunity which may be maintained at a high level when recall doses are given. This is perhaps best illustrated by the experience in the armed forces in regard to tetanus which was virtually eliminated in the recent war, one of the brilliant achievements of preventive medicine. The essence of this success lay in the fact that a recall dose of toxoid was accepted as a routine procedure. The unpublished results of tetanus antitoxin titrations of blood samples of some 2000 members of the armed forces indicate that all who had received the routine inoculations of toxoid, including the annual recall dose, showed a protective level of antitoxin ($>1/100$ u/cc). In contrast, in a small group of 53 who had not had a recall dose, only 62 per cent showed antitoxin at or beyond this level.

The effectiveness of minute doses of diphtheria antigen when given as a secondary stimulus is illustrated by the fact that a Schick test with control of diluted toxoid will produce a conversion from Schick positive to Schick negative in approximately 70 per cent of persons. The combined value

of the test toxin plus control is only 0.021 Lf. A secondary stimulus of Schick test toxin alone which represents only 0.001 Lf may give on the average a tenfold increase in antitoxin. To a group of twelve persons, all of whom possessed antitoxin initially, a secondary stimulus of 4 Lf of toxoid was given and blood samples taken daily for one week and at longer intervals thereafter up to six years. The first detectable increase in antitoxin was manifested by the fourth day; by the seventh day all had responded and the maximum titre was attained by the majority by the eleventh day. The highest level recorded in this small group was 120 units per cc. of serum. In a group of 340 persons, 95 per cent showed a response to toxoid when given as a secondary stimulus. These and similar studies were undertaken to determine the minimum, and at the same time practical, recall dose and to follow the level of antitoxin over a period of years. In general, the response in antitoxin varied with, though not in direct proportion to, the strength of the stimulus. In pre-school children where sensitivity to toxoid is not a problem, a recall dose of 20 to 40 Lf is desirable. In school populations, in order to avoid the necessity of a preliminary sensitivity test, 3 or 4 Lf of toxoid, because of its freedom from untoward effects and the satisfactory degree of antitoxin response, may be recommended as a recall dose. A similar dose is effective in adults, but except in the face of an epidemic, screening by a reaction test for sensitivity is desirable.

The rate of loss of antitoxin as already mentioned is subject to wide individual variation. On the average, in a non-diphtheria environment, there is a loss in antitoxin of 60 per cent within two years as shown in a group of children studied in 1937. That is to say, taking the average antitoxin level of a group of immunized children as 0.33 u/cc, the average unitage has dropped to 0.13 u/cc in two years. Other studies have shown that from 10 to 30 per cent of persons revert to Schick positive within three to five years. It is quite apparent then that no success in the control of diphtheria may be expected without the recall dose.

The quality of toxoid is adequately safeguarded by the National Institute of Health. One may thus generalize by saying that any diphtheria toxoid given in two or three doses with an interval of three to six weeks may be expected to act as an effective primary stimulus. A recall dose given six to twelve months later will result in a protective level of antitoxin in well over 90 per cent. Without at least one recall dose the immunization procedure must be regarded as incomplete. In children immunized in infancy a second recall dose is recommended between the ages of eighteen and twenty-four months and a third when the child enters school. Possibly the second may be omitted, but because of the increased hazard of school a dose should be given at this time. In older children a booster dose is recommended every four or five years. In the armed forces approximately 50 per cent were Schick positive. In the recent epidemic at Halifax 45 per cent of cases were over fifteen years of age. Before diphtheria is effectively controlled adults will be required to be immunized. The administrative difficulties as well as the problems of reactions to toxoid are obvious. A preliminary screening with a Schick test and control of diluted toxoid (0.2 Lf/cc) which serves also as a "reaction test" is essential. Following this scheme, some hundreds of thousand personnel of the Royal Canadian Air Force were inoculated against diphtheria.

The use of multiple antigens will in some measure reduce the administrative burden of immunization. In a small series of very young children the response to diphtheria and tetanus toxoids was particularly striking after four doses of these antigens with pertussis vaccine added. There is good laboratory evidence to show that the bacterial element acts as an adjuvant.

With 600,000 cases of diphtheria per year reported in Europe there is no basis for complacency. Nothing less than a vigorous campaign of active immunization with a schedule of inoculations possibly more rigorous than necessary, is required to offset the menace of diphtheria in America.

*Immunization of Adults with Diphtheria Toxoid**

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Although immunization of children in the first years of life is rarely attended by serious reactions, the proportion of undesirable reactions following administration of diphtheria toxoid rises markedly with increasing age. These reactions in the older age groups may consist of severe local swelling with edema and tenderness accompanied by fever and malaise and are analogous to those caused by the injection of relatively large amounts of tuberculin into tuberculous individuals.

The more severe reactions to the subcutaneous injection of large amounts of toxoid, as well as the pseudoreactions observed in the Schick test have been variously ascribed to (a) constituents of the culture media, (b) to diphtherial bacillary proteins other than toxin or toxoid, (c) to toxin or toxoid itself. It is of practical importance to determine which of these constituents of the formalinized culture filtrates cause undesirable reactions in sensitive individuals. This is of particular importance at the present time because of the marked increase of the incidence of diphtheria among the older age groups.

We have, therefore, studied the reactions of adults to certain formalinized protein fractions from culture filtrates of the diphtheria bacillus. The materials used have consisted of:

1) A formalinized mixture of atoxic diphtherial proteins, hereafter called the P-fraction, which contains less than 0.03 per cent toxoid.

2) Highly purified diphtheria toxoid esti-

mated to contain less than 5 per cent P-fraction or other nitrogenous material, prepared from highly purified diphtheria toxin previously shown to be homogeneous by physicochemical and immunochemical methods.

3) Crude toxoid prepared from toxic filtrates of organisms grown on a chemically defined medium and containing about 65 per cent P-fraction and 35 per cent toxoid.

The possibility of reactions caused by broth constituents has been eliminated by cultivation of the organisms on the peptone-free, chemically defined medium of Mueller and Miller.¹

By means of two sensitive biological tests, the precipitin reaction and active and passive anaphylactic response in guinea-pigs, it has been demonstrated that purified diphtheria toxoid and P-fraction are immunologically distinct, one from another.

One hundred and eighty-six medical students and nurses were Schick tested with Schick toxin prepared by the New York City Bureau of Laboratories. Purified toxoid and P-fraction diluted to Schick strength in borate buffer containing 0.02 per cent gelatin were used as controls.

The reactions observed were found to fall into eight distinct categories exclusive of occasional reactions attributable to the stabilizing agents present in the diluents. Individuals may be Schick positive and show allergic reactions of the delayed tuberculin type to either P-fraction or toxoid, to both, or to neither. Similarly, individuals in the Schick negative group may be aller-

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gic to either fraction, to neither, or to both. Thus the materials show the same specificity in the human as shown by precipitin tests and anaphylaxis in the guinea-pig.

Among the Schick positive group only 3 of 58 were highly sensitive to purified toxoid. The sensitive individuals show some circulating antitoxin (ca 1/200 unit/cc.). Almost all of the Schick positive group, however, showed sensitivity to P-fraction and crude toxoid provided they were injected in high enough dosage. It is obvious, therefore, that the use of purified toxoid (purified especially with respect to P-fraction) rather than crude toxoid for immunization of most but not all Schick positive individuals should possess distinct advantages.

Since approximately 30 per cent of the Schick negative individuals showed allergic reactions to the toxoid itself diluted to Schick strength, we must conclude that even if toxoid were completely freed from last traces of impurity, its administration undiluted to an adult population without preliminary screening tests would result in a very high proportion of undesirable general reactions.

The Schick positive group were immunized with three doses of the purified fluid toxoid (0.002 cc. or 0.2 cc., 1 cc. and 1 cc.) administered at 3-week intervals. Because of preliminary screening out of sensitive individuals by means of reactions to the Schick test, no significant local or general reactions were encountered.

The antitoxin levels were followed during the course of immunization. Analysis of the results has indicated that delayed allergic reactions of the tuberculin type to either

P-fraction or purified toxoid are indicative of "latent immunity." Allergic individuals of this type, particularly those sensitive to toxoid itself show a large anamestic response following injection of even very small doses of purified toxoid (0.002 cc or less).

This work has led to the conclusion that purified diphtheria toxoid provides a distinct improvement over the crude toxoid in current use. However, its advantage is limited essentially to Schick positive individuals showing no sensitivity. Since a high proportion of Schick positive adults show evidence of "latent immunity" to diphtheria and produce a high titre of antitoxin in response to very small doses of toxoid (see also Edsall²), it is questionable whether immunization of older children and adults with the full dosage is necessary or advisable in most cases. It is of interest in this connection that of 81 Schick positive medical students and nurses Schick tested with purified diphtheria toxin and with 0.0002 cc. (0.008 Lf) of purified toxoid as control, only 37 (45.7 per cent) were still Schick positive when retested one month later. The full immunizing dose of undiluted purified toxoid can be injected into these Schick positive individuals after the second Schick test without fear of undesirable reactions.

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



JUNE 1948

TESTICULAR DYSFUNCTION *

E. PERRY McCULLAGH

Cleveland Clinic, Cleveland, Ohio

THE testis is composed of two main parts and has two main functions. The tubule creates the male gamete, the spermatozoon, and nourishes it till it passes to the epididymis where it is stored and matures from a state of relative immotility to motility. The interstitial cells lie in compact groups between the tubules. They produce the male hormone which has many important effects, spermatogenic, masculinizing, and metabolic. In the immature testes the tubular cells are crowded, undifferentiated and the tubule not laminated. Leydig cells are poorly developed and simulate the fibroblasts from which they develop. The adult Leydig or interstitial cells lie in discrete masses in the intertubular spaces. These cells vary greatly in size, and have large granular nuclei. The smaller cells are elongated, the larger ones ovoid or polyhedral and are 20 or more microns in diameter. The larger cells have pale areas in their cytoplasm which appear to grow with the aging of the cell and form vacuoles. In their cytoplasm lie rod-shaped crystalloids and granules which react chemically as neutral fats and steroids. In the adult the tubule is composed of a thin basement membrane through which all nutriments must pass to the intertubular cells. Within the tubule are

* Given October 16, 1947 at the 20th Graduate Fortnight of The New York Academy of Medicine.

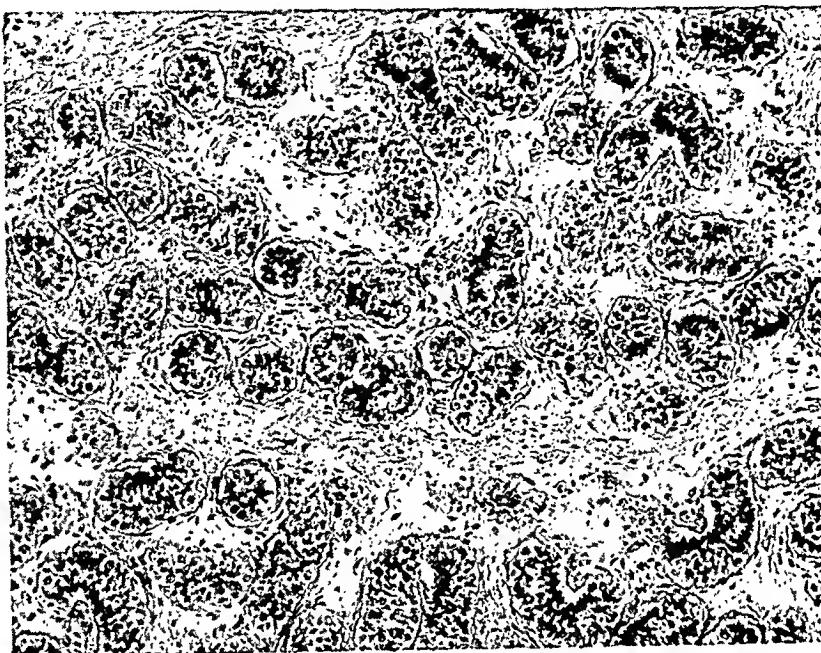


Figure 1. Normal testis of a boy 8 years and 10 months of age.



Figure 2. Normal adult testis, showing abundant active Leydig cells. Normal tubules and active spermatogenesis.

TABLE I
NORMAL URINARY GONADOTROPHINS IN BOYS AND MEN

<i>Age (in years)</i>	<i>F.S.H. (mouse units) per 24 hrs.</i>	<i>Number Of Subjects</i>
2½—10	<.6	2
	6.6—13	5
10—12	<6.6	2
	6.6—13	2
12—15	13—105	20
20+	26—105	22

long flame-like syncytial masses, the Sertoli cells, with indented nuclei near their bases. These nourish the spermatocytes throughout their development and in them the young sperm bury themselves before entering the tubular lumen. The spermatogonia lie near the periphery of the tubule and pass through the phases known as primary and secondary spermatocytes changing to small round dense spermatids gradually assuming the tail and final shape of a mature spermatozoon.

The hormones which control the testes are chiefly from the anterior lobe of the pituitary gland and arise there in the basophile cells. Two gonadotrophic hormones are considered to exist. One stimulates the development and function of the interstitial cells. It has not been adequately measured in man nor its normal levels defined. The second stimulates spermatogenesis and is often referred to as follicle-stimulating hormone or F.S.H.* since its biological activity is frequently measured by its power to stimulate follicular function and uterine growth in immature female animals.* It can be readily shown that the level of F.S.H. in human urine rises rapidly at puberty into adult levels (Table I).

The interstitial cells under the impact of gonadotrophin produce androgen or male sex hormone, which is considered to be testosterone, though this steroid has not been proved to exist in any testis except

* Urinary gonadotrophins referred to in this paper are measured in mouse units and represent tests done by the method of Knobil, H. F., Jr., Albright, F., and Griswold, G. C., *J. Clin. Endocrinol.*, 1943, 3:529.

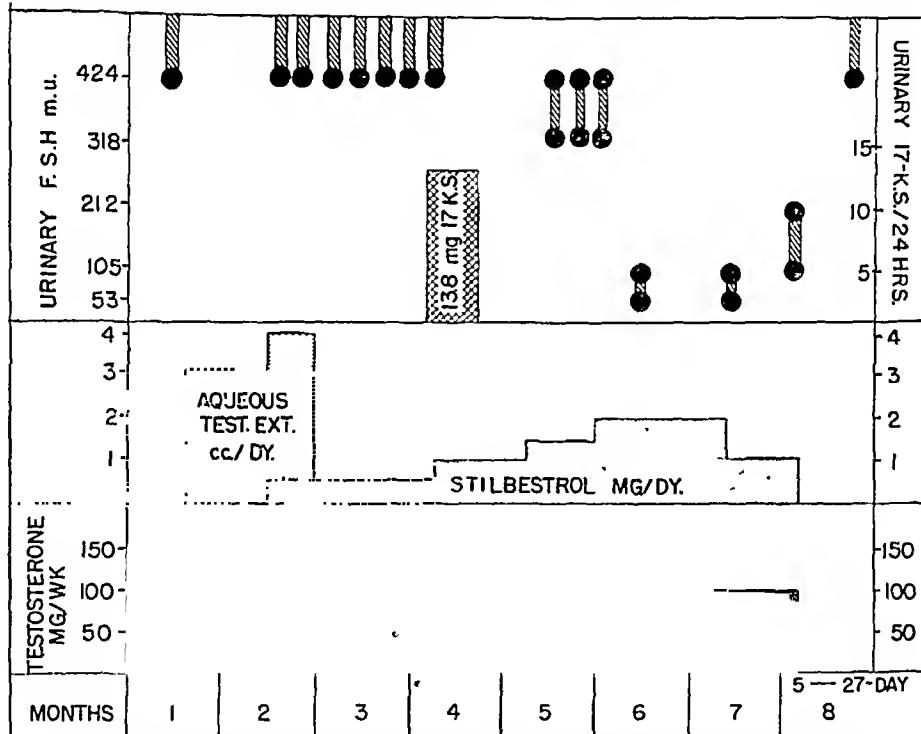
TABLE II

NORMAL URINARY ANDROGENS PER 24 HOURS IN MEN

Assay	Range	No. of Assays	No. of Subjects
Androgens (capon)	14-122 units	41	20
17-K.S. (ketonic fraction)	6-16 mg.	48	48

TABLE III

INABILITY OF TESTOSTERONE TO INHIBIT PITUITARY



TESTOSTERONE AS PROPIONATE I.M. 150 MG. PER WEEK OR MORE FOR 5 MONTHS PRECEDING TIME SHOWN

that of the bull. Biologically androgen may be measured in a variety of ways, one of which is based on its power to cause growth of the capon's comb. An indirect estimate may be made by the chemical determination of 17-Ketosteroids,* part of which are of adrenal origin.

* Urinary 17-Ketosteroids are measured on a pure ketonic fraction and done by a modification of the Holtzendorf method. Extraction is done by aluminum hydroxide adsorption.

Judging from analyses made in the case of an interstitial cell tumor,¹ the 17-Ketosteroids of testicular origin are androsterone, etiocholanolone, isoandrosterone, and Δ^2 -androsterone-17.

Testosterone is essential for the growth and maintenance of the entire genital system apart from the interstitial cells themselves. This probably includes the tubules. It certainly includes the vas deferens, prostate, seminal vesicles, accessory urethral glands, penis and scrotum. It is largely responsible for the appearance of such male characteristics as body hair, beard and laryngeal growth, and is intimately connected with male baldness. It stimulates sex drive, causes nitrogen and electrolyte retention, muscle growth and helps to maintain the basal metabolic rate and red blood cell level typical of the male. It is intimately connected with typical male aggressiveness, vigor and tendency to fight.

Castration before puberty prevents the development of the genitalia and secondary sex characteristics. After puberty atrophy of the accessory genital glands occurs. Castration also causes marked alteration in the anterior lobe of the pituitary gland including hypertrophy, enlargement of the basophile cells with eventual vacuolization and the formation of the so-called signet-ring or castration cells. In animals, such pituitary glands contain an excess of F.S.H., as shown by experimental implantation, and the urine under such circumstances contains an excess of this hormone rising in men to 200 to 500 mouse units in 24 hours. Withdrawal of androgen from the body does not explain this effect. Loss of androgens, as in Addison's disease in women,² is followed by excessive F.S.H. excretion. In men with severe testicular failure doses of testosterone in amounts which raise the 17-Ketosteroid excretion to high levels, frequently do not inhibit excessive F.S.H. excretion.

Tubular failure in man such as occurs in cryptorchidism (Fig. 3) or after x-ray damage to the testis, or oligospermia from other causes is followed by high F.S.H. excretion without castration effects in the prostate and with normal levels of androgens and 17-Ketosteroids in the urine. In animals with vitamin E deficiency damage to the tubules causes hypertrophy and castration changes in the pituitary gland and a high pituitary content of F.S.H., with little or no evidence of loss of androgens as judged by prostatic size.³

There are two schools of thought regarding the mechanism involved. Our group has favored the idea that there is a second testicular hormone formed in the germinal epithelium, the withdrawal of which

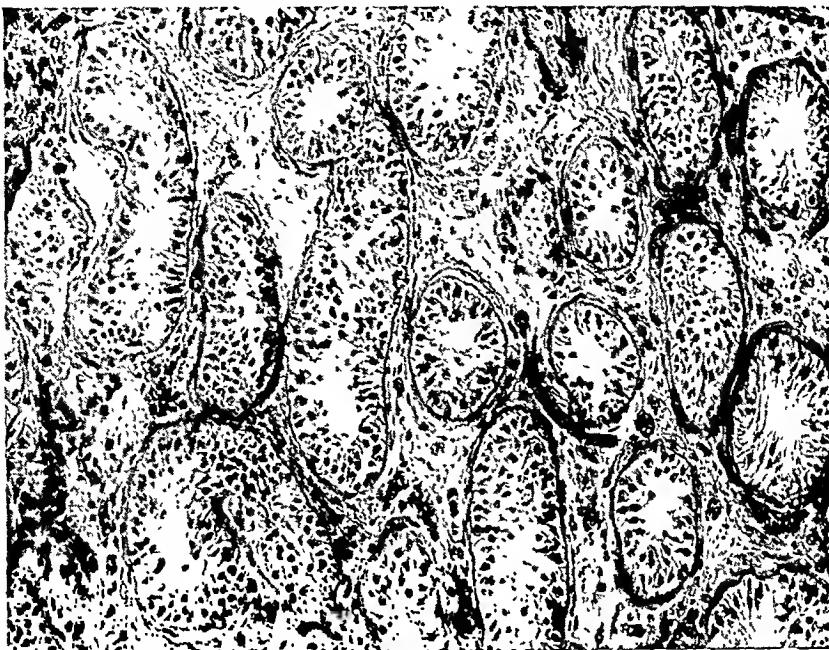


Figure 3. Cryptorchid testis of a youth 17 years of age. Tubules are comprised almost entirely of Sertoli cells. There is moderate thickening of the basement membrane. Small islands of Leydig cells are present.

results in heightened pituitary function, while Dr. Carl Heller favors the idea that the excessive excretion of gonadotrophins is due to the lack of utilization of these substances by the tubular cells.

Primary testicular hyperfunction is a condition so rare as to deserve little attention. When a functioning tumor of the Leydig cells arises before puberty, as in the famous case of Sacchi,⁴ abnormally rapid genital and somatic growth occurs. The clinical picture then is similar to that seen in pubertas praecox associated with adrenal cortical tumor.

Primary testicular hypofunction usually refers to deficiency of the Leydig cells and is hypoandrogenism. It is a relatively common condition. It is almost invariably associated with severe tubular failure. There are apparently rare exceptions to this. I have seen one patient who is one of two brothers with severe eunuchoidism. His testes approached normal size and, although biopsy showed that spermatocytes were present and relatively healthy in the testes, Leydig cells were rare.

(a) In infancy, testicular deficiency may be suspected because of very small genitalia, but unless severe testicular atrophy can be proven, the diagnosis is not usually suspected until there are evidences of delayed puberty. Marked growth of aplastic infantile genitalia, such

as was demonstrated by Lisser,⁵ probably demonstrates only the inherent ability of such infantile organs to respond to androgens and does not prove a pre-existing androgen level below normal for that age.

(b) Hypogonadism in adolescence. The question of delayed puberty frequently arises in connection with obesity in boys between the ages of 11 and 15 years. Accurate diagnosis is usually not easy. Many such boys are quite normal apart from the obesity. It should be kept clearly in mind that the penis normally grows little between infancy and puberty, and, in addition the appearance of hypoplasia at first glance, may be found on careful examination to be due entirely to the fact that the genitalia are buried in surrounding fat. Familial factors in obesity are sometimes apparent because of the striking similarity of parent and child. In some boys at the age of 11 to 13 years, in spite of the obesity and other characteristics previously assumed to be of pituitary origin, there may be found to be a distinct early growth of pubic hair. This is good evidence of increasing androgen production and impending normal puberty. The fact that such patients may respond with rapid genital growth to injections of pregnancy urine extract is comparable to the response of infantile genitalia to testosterone and does not prove a previous testosterone deficiency. In many instances the use of a 1200 calorie diet, aided, perhaps, by amphetamine, may be more desirable therapy.

By the age of 14 or 15 years obesity may be associated with fairly evident delay in puberty. Such patients should not be classed as Fröhlich's syndrome unless they have a suprasellar tumor. Adiposogenital dystrophy is a preferable term, though its connotation is not very different. Apparently the majority of such boys have no pituitary deficiency. We did assays on three groups of 20 representative cases in each group. One group was classed as simple obesity, in the next delay in puberty was strongly suspected, and in the third, it was considered definite. It was found that only 3 boys over 12 years of age in this group of 60 patients had presumptive evidence of pituitary deficiency on the basis of assay. The assays were done more than once in every patient in whom the first test was below 6 mouse units. In some, increased titers of gonadotrophins indicated pituitary hyperactivity and suggested strongly a primary testicular failure as a cause of the pituitary hyperfunction, due to poor ability of the testes to respond to the increased stimuli.

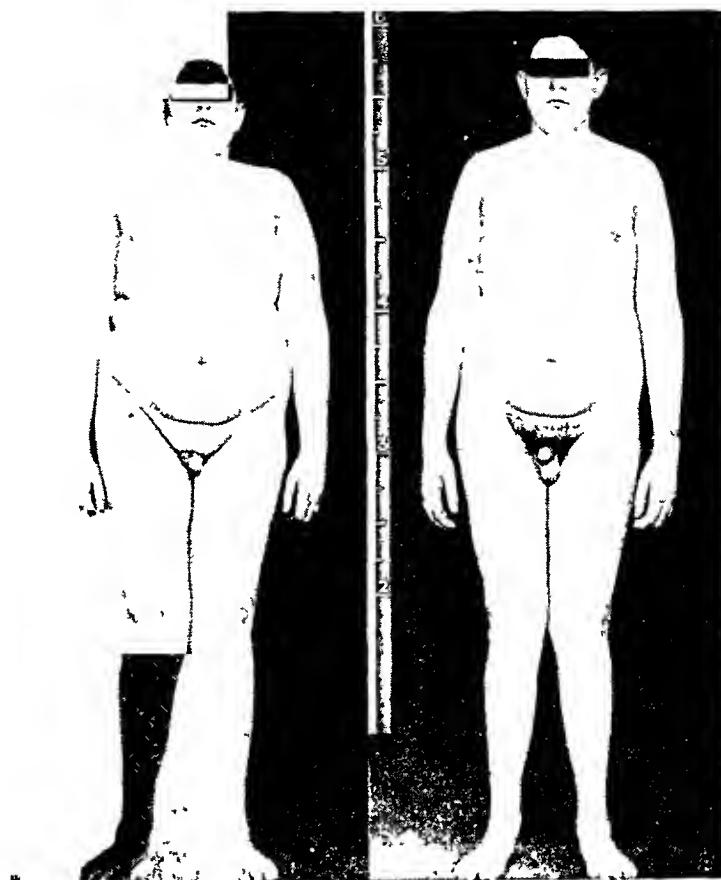


Figure 4. Adiposogenital dystrophy—age 14. Showing effects of chorionic gonadotrophin 500 I.U. three times weekly for 21 months.

The mechanics which may explain this situation are not clearly understood. Because distinct gonadal deficiency is known to follow marked overfeeding in animals⁶ and in view of the normal or high urinary F.S.H. usually found in obese boys with delayed puberty, I am inclined to believe the syndrome is one of hypothalamic disorder with excessive appetite, obesity, and consequent testicular deficiency. The response of such patients (Fig. 4) to diet and chorionic gonadotrophin injections may be excellent. In what proportion spermatogenesis is normal in later years is not yet known. In a few we have examined, it remains defective. In some boys hypogonadism is associated with abnormally short stature though no pituitary deficiency can be proven and urinary F.S.H. is normal. Treatment with chorionic gonadotrophin may result in great increase in growth.



Figure 5. Typical eunuchoidism—age 18. Height 71½ inches, span 77½ inches. Testes: navy bean size. Genital development and puberty retarded. Sella turcica normal. 17-K.S. 3.4 mg./dy. F.S.H. 103 m.u./dy.

PREPUBERAL CASTRATION OR EUNUCHISM AND LESS SEVERE PREPUBERAL LEYDIG CELL FAILURE OR EUNUCHOIDISM

The clinical picture of classical eunuchism is a familiar one. Typically (Fig. 5) the patient appears as a rather tall, slightly pale, beardless person whose facies give a peculiar expression of a mixture of youth and age. The immature facies, the beardlessness, the high pitched voice together with the quiet demeanor usually present, gives the impression of femininity. Physical examination shows the penile development of childhood, a small scrotum, usually small testes which may be diffusely soft or discrete and very hard. Scant axillary and pubic hair are present. There is no recession of the temporal hair line, and body and limb hair otherwise are largely lacking. The muscles

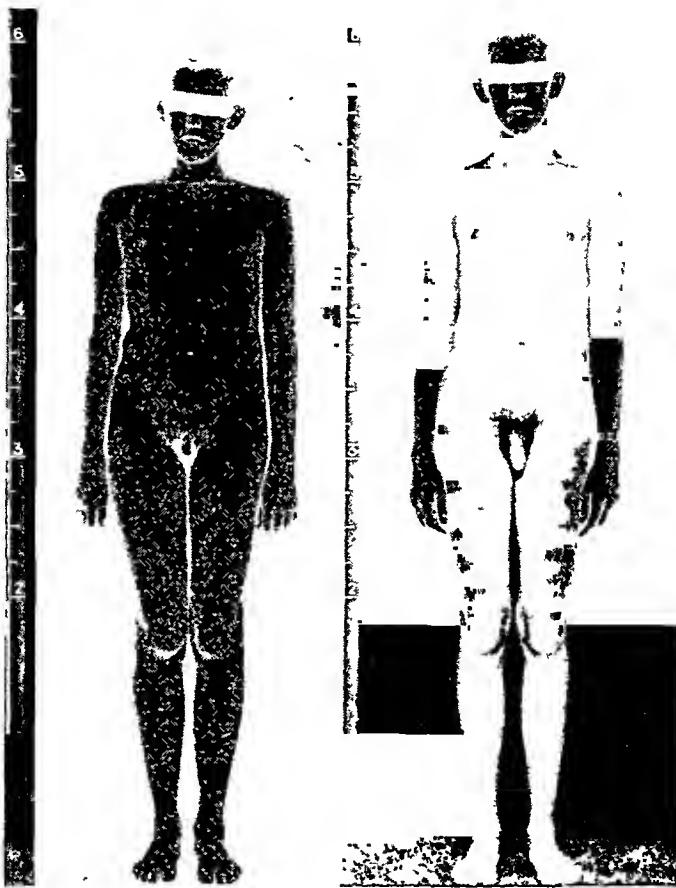


Figure 6. Eunuchoidism—age 21. 17-K.S. 37 mg./dy. Urinary gonadotrophins >424 m.u./24 hrs. The change shown represents testosterone therapy at approximately the rate of 25 mg. 3 times weekly, for one year.

appear flabby and never stand out in relief as they may in a well-trained athlete. Although weakness is difficult to prove, such an individual could scarcely be expected to be an asset to a varsity crew (Fig. 6). The arms and legs, hands and feet are elongated, producing the typical eunuchoid proportions in which the span may exceed the height by 4 or more inches and the distance from the top of the pubis to the soles be greater than half of the total height. Epiphyseal lines have been seen under these circumstances to be open up to 42 years of age. The mild reduction in basal metabolic rate which occurs is demonstrated by the average in 15 of our patients with eunuchoidism of moderate to severe degree. The average was -16.6 per cent.

THE ETIOLOGY OF PREPUBERAL TESTICULAR FAILURE, ESPECIALLY CONGENITAL FACTORS

The cause of eunuchoidism is often obscure. Mumps' orchitis is apparently the most common cause. Occasionally severe swelling of the testis occurs with pain and fever unresponsive to the sulfonamides or penicillin. There may be no other clinical suggestions of mumps. The process may last for 4 to 6 weeks, followed by marked atrophy of one gland and recur as long as a year later in the opposite testis. Bacterial infection is not a frequent cause of lasting androgen deficiency and is rare before puberty in any case. Other bacterial toxins, surgical or accidental trauma may be the cause.

Congenital factors apparently are more common than formerly suspected. Attention is called to this possibility when eunuchoidism is present in brothers. At times associated endocrine disorders occur, such as dwarfism, hypothyroidism and eunuchoidism, as are present in three brothers in our series of cases. Eunuchoidism of severe degree has been seen in two cousins and a paternal uncle. In another instance which suggests strongly a milder degree of the same tendency, I have observed eunuchoidism in one brother and oligospermia without eunuchoidism in the other.

In some cases the congenital factors involved appear more evident since there are other and perhaps multiple congenital defects present. Such may be the case in some instances of Laurence-Moon-Biedl syndrome. In others, however, no Leydig cell failure exists. The following patient is an example of eunuchoidism associated with congenital defects.

The patient (Fig. 7) is 35 years of age, short in stature, being 62 $\frac{1}{2}$ inches in height. He showed unmistakable evidence of severe androgen deficiency. Urinary 17-Ketosteroids were 4.9 mg. and urinary F.S.H. within normal range, namely 6 to 105 mouse units in 24 hours. In addition, the posture was stooped, apparently due to dorsal kyphosis. The abdomen was prominent, and the abdominal muscles weak. The hands were of a peculiar shape due to the fact that the terminal phalanges were constantly flexed. There was a speech defect of the cleft palate type. Ears lacked the usual peripheral roll. Bilateral inguinal herniae were present, and the scrotum was empty. A mass presumed to be the right testis was palpable in the groin. The prostate was



Fig. 7



Fig. 8

Figure 7. Eunuchoidism of congenital origin. See text.

Figure 8. Eunuchoidism with gynecomastia—age 33. Sella normal. 17-K.S. 8.6 mg./24 hrs. Urinary gonadotrophins 318-424 m.u./24 hrs. Attempted testis biopsy yielded no testis tissue. At mastectomy, the tissue removed contained much fat with a central area of soft greyish tissue. This on microscopic examination showed loose fibrous tissue with sparsely placed ducts.

two-thirds normal size. A biopsy of the mass thought to be the right testis showed only epididymis. Since this is the only occasion in approximately 250 testicular biopsies by the same surgeons that such a report has been given, it seems reasonable to believe that the testis was congenitally absent in this patient.

In another patient, a severe eunuchoid 75½ inches tall, congenital factors were strongly suspected because of the marked webbing of the neck present. His urinary 17-Ketosteroids were 5.9 mg. per 24 hours and F.S.H. was 105 m.u. on one occasion and 212 to 318 m.u. on another. The testes showed large swollen and abnormal Sertoli cells and absence of spermatocytes. No Leydig cells were evident.

GYNecomastia AND THE TESTIS

Small solid tender masses of breast tissue beneath the areolae frequently occur during adolescence and are usually of only a few weeks' duration, disappearing completely. A similar or more diffuse but evanescent type of breast enlargement may occur in men past middle life.

Gynecomastia and persistent lactation can occur in men with pituitary tumor, indicating clearly that the pituitary secretions may cause this condition. Rather striking gynecomastia is often seen in men taking stilbestrol for carcinoma of the prostate. In light of these facts it is impressive that gynecomastia may also follow the use of testosterone propionate injections and is even more frequent and more marked after methyl testosterone orally.

Fairly marked gynecomastia occurs in some eunuchoid individuals (Fig. 8), and Heller and Nelson⁷ have called attention to the fact that those with a nearly normal body habitus are more likely to show gynecomastia than those with eunuchoidal proportions. Klinefelter⁸ claims that such a condition occurs without any androgen deficiency and explains it on the basis of loss of hormone from the tubular epithelium. Despite normal 17-Ketosteroid assays, the appearance of these patients suggests the presence of androgen deficiency.

EFFECTS OF CASTRATION IN THE ADULT

Apart from sterility the chief effects of castration in man are atrophy of the prostate and a striking increase in gonadotrophins in the urine. The second effect is almost certainly associated with the same type of pituitary change known to occur in animals. There is almost no regression of secondary sex characteristics when they are already established. Thus beard, voice, body hair, penile and scrotal size remain essentially unchanged. Potency is usually reduced and sometimes eradicated. In those individuals whom I have examined, energy appears to be low. Most individuals castrated are ill because of carcinoma or tuberculosis, and for this reason the effects of castration upon weight, B.M.R., blood count and chemistry are difficult to estimate.

The symptoms following castration vary greatly. In some patients they are insignificant. In others nervous irritability, restlessness, a

tendency to depression, and hot flashes similar to those seen at the female menopause, may be sufficient to distract from mental work and interfere with sleep. The fact that castration may produce so few symptoms in some men points clearly to the necessity of caution in making a diagnosis of male climacteric, especially when testicular deficiency has not been proved to exist.

THE MALE CLIMACTERIC

The term male climacteric is a poor one because it implies that functional testicular failure sufficient to cause symptoms is a physiological process in men. Such has not been shown to be the case.

Such symptoms as "nervousness," "irritability," "lack of confidence," "sense of futility," and "depression" which are mentioned in the literature are certainly of a diffuse sort and all too often when ascribed to male climacteric may be in reality the result of increasing fatigue in an aging man whose business and social responsibilities have increased beyond the tolerance of his nervous system. Sexual impotence when due to androgen deficiency responds promptly to testosterone. Unfortunately for impotent men, androgen deficiency is a relatively rare cause of their complaint.

Apparently in men beyond 50 years of age, a functional gonadal failure occasionally occurs and is sufficient to cause symptoms. At present, however, there is no thoroughly satisfactory means of establishing a diagnosis.

If the condition is suspected because of otherwise unexplained nervous symptoms, fatigue, impotence, and hot flashes, it may be desirable to try to corroborate or refute the impression.

Unless impotence is extreme a semen examination can be done. A count below 100 million with less than 25 per cent motility is probably abnormal. A normal count argues strongly against the diagnosis. It should be kept in mind that a moderate decrease in motility of sperm is consistent with the normal for advancing age.

Gonadotrophin assays may be of some value. There is apparently no normal increase in urinary gonadotrophins in older men as shown in Table IV. Table IV shows assays done consecutively in a group of men only mildly incapacitated with various diseases. It seems inconsistent with the physiological facts that climacteric symptoms could exist in the absence of high urinary gonadotrophins. High levels are

TABLE IV
URINARY GONADOTROPHINS IN OLDER MEN

<i>Age</i>	<i>Assay</i>	<i>Diagnosis</i>	<i>Age</i>	<i>Assay</i>	<i>Diagnosis</i>
50	26—53	Fatigue	63	13—53	Petit mal
51	13—26	Hypertrophic arthritis	63	13—53	Apoplexy
54	105—212	Hypertrophic arthritis	64	13—105	Fatigue
55	53—105	Retinal detachment	64	13—105	Hypertrophic arthritis
56	13—105	Irritable colon	65	13—52	Hypertrophic arthritis
56	13—105	Psychoneurosis	66	26—53	Old fractures pain
59	13—53	Graves' disease	67	26—53	Parkinson disease
60	26—53	Cataract	68	53—105	Hernia. Senile keratoses
60	6—13	A.S.H.D.	80	26—53	Cataract
60	13—105	Diabetes			

TABLE V
URINARY GONADOTROPHINS AND 17-KETOSTEROIDS IN MEN
WITH OLIGOSPERMIA

<i>Case</i>	<i>Rat Assay</i>	<i>M.U.</i>	<i>17-K.S.</i>	<i>Sperm Count</i>
1	81	480—633	2, 8	Occasional
2	82, 74	288—284	11, 13, 10	Occasional
3	64	105—212	11, 7	Few
4	89, 79	105—212	10	1
5	78	105—212	14	1
6	89, 79, 75	105—212	10	1

Rat uterine weight in normal uninjected animals weighing between 30 and 40 mg.—
17—21 mg.

TABLE VI

MALE CLIMACTERIC 17-KETOSTEROIDS—38 ASSAYS—35 CASES

<i>mg./24 hr.</i>	<i>Cases</i>	<i>Assays in Cases improved on therapy</i>
1—2	2	
2.1—3	1	
3.1—4	7	3.1
4.1—5	9	1.1
5.1—6	4	4.0
6.1—7	9	8.0
7.1—8	1	
8	1	
10.9	1	

TABLE VII

MALE CLIMACTERIC

	<i>Mouse Test</i>	<i>Rat Test</i>	<i>10 Improved Cases</i>
High	18	6	6
Number	15	3	2
Total	33	9	

well known, however, to be at times the result of oligospermia in younger men completely free of symptoms. A few representative cases of this type are shown in this chart.

Recently we have done 17-Ketosteroid assays 38 times in 33 patients suspected of male climacteric—only 3 were strictly normal, 9 were borderline (6.1 to 7 mg./24 hrs.) and 23 were low. Gonadotrophin assays were done 42 times and were found high in 24. These findings seem consistent with the fact that such individuals have male climacteric. In a group of 66 patients treated, we were satisfied in only 10 that the response obtained was equal to that seen in known hypogonadism. In them, however, relief of symptoms was prompt and complete. At present in clinical practice it seems reasonable to assume that symptoms are not due to male climacteric in men with normal

TABLE VIII

TWO CASES OF ACROMEGALY WITH HIGH URINARY F.S.H. AND GOOD SPERM COUNTS

Age	Semen Examination			F.S.H.	Remarks
	total million	per cc. million	motility	m.u./24 hrs.	
52	430 million	70 million	50% 4+	106-212	Potence normal
				106-212	Prostate normal
41	236 million	40 million	20% 4+	106-212	Potence slightly reduced
				106-212	Prostate normal
				106-212	

F.S.H. and normal sperm. If investigation of a more complete type is not available and the condition is suspected, a therapeutic trial of testosterone therapy is warranted. True climacteric symptoms may be expected to disappear within three weeks on adequate treatment.

TESTICULAR DISEASE OF PITUITARY ORIGIN

Pituitary Hypergonadism. True hyperactivity of the testes as a result of pituitary hyperfunction has never been shown to exist. It is possible, however, for the pituitary to secrete more than normal quantities of gonadotrophins because of a disorder within itself and not necessarily because of testicular failure. This happens occasionally in acromegaly.

It is true that in long standing acromegaly, testicular failure frequently exists. When it does it stands as a possible cause of high F.S.H. if this is present. The F.S.H. was abnormally low in the urine of 6 of 10 cases of acromegaly studied by Klinefelter⁹ and abnormally high in none. In 6 of our cases, 3 showed high levels and in 2 of these there was a good testicular response. This, then, seems to be as close an approach to hypergonadism of pituitary origin as can be demonstrated.

Pituitary Hypogonadism. In the past the diagnosis of pituitary gonadal deficiency was relatively common. Recently, however, since such an impression has almost always been checked with assays for gonadotrophins, in my practice, my ideas have changed. The impression

continues to grow that, although functional pituitary deficiency of clinical significance may sometimes occur, it is seldom present apart from such disorders as severe anorexia nervosa or in organic disease of the anterior lobe, such as exists in Simmonds' disease, pituitary or parasellar tumor.

The accurate clinical diagnosis of pituitary hypogonadism during adolescence usually depends first upon suspecting the disease, perhaps because of shortness of stature, and secondly on the demonstration of a local lesion by x-ray and visual field studies. If these findings are equivocal, assays may be very important aids. Urinary 17-Ketosteroids of less than 2.0 mg. and gonadotrophins less than 6 mouse units in patients over 13 years of age may be the most important diagnostic data available.

Under such circumstances obesity is seldom present and true Fröhlich's syndrome is rare. The commonest cause is craniopharyngioma. The condition can be closely simulated by chronic hydrocephalus. If there are unbearable headaches or progressive visual loss, surgical attack upon the pituitary is warranted. If treatment for the local lesion is unnecessary body growth can be stimulated and sexual development accelerated by the use of chorionic gonadotrophin, testosterone or both. Postoperatively much improvement in testicular health may occur.

In adults a similar situation may be caused by craniopharyngioma, a chromaphobe or sometimes eosinophil adenoma, local trauma or sometimes a carotid aneurysm.

In addition to severe testicular damage, clinical evidence of thyroid and adrenal deficiency frequently exists. The B.M.R. may be very low, insulin tolerance is increased, the water excretion test is positive and the urinary 17-Ketosteroids about 1.0 mg. or less—much lower than in castration and as low as that seen in myxedema or in Addison's disease² in women. A tumor, if present, must be treated on its own merits. Medically, testosterone gives much more benefit than other hormones. Adrenal cortical extracts, desoxycorticosterone and thyroid are of very limited value. When pituitary surgery is necessary, extra support to the patient with large doses of adrenal cortical extract is warranted.

In rare instances a slowly progressive glial tumor such as oligodendrogloma may produce marked testicular failure. As it progresses

hypothalamic symptoms occur and as drowsiness and diabetes insipidus increase, extreme cachexia precedes death.

It is interesting that in Cushing's syndrome, supposed by some to emanate from the basophile cells of the pituitary (sex hormone producing), we have demonstrated completely normal levels of F.S.H. and of 17-K.S. in the urine.

TUBULAR FAILURE

Some of the hormonal aspects of tubular control and tubular failure have already been mentioned. Time will not permit more than a few cursory remarks regarding semen examination and the value of testicular biopsies in the study of sterility.

In studying a childless couple the semen is one of the most important items, since it is abnormal in almost 50 per cent of instances of childlessness. If a careful history and physical examination are normal, semen is best obtained by masturbation at the office, or if not, by coitus interruptus. The semen should not be placed in a condom but ejaculated into a clean glass bottle and under no circumstances should an attempt be made to keep it warm. An interval of 4 days between the time of previous coitus and the obtaining of the ejaculate for examination is standard. The specimen should reach the laboratory promptly, although examination should not be attempted for 20 to 30 minutes after ejaculation, to allow for liquefaction to occur.

The details of laboratory technique cannot be included now. A brief view of what is considered normal and abnormal may be had in Table IX.

In a recent survey of 500 consecutive semen examinations in childless couples, 100 were selected in whom a definite fault was found in the wife and none was evident in the husband. Some of the outstanding characteristics of these counts were compared with those in 200 childless husbands whose wives were normal. A judgment of normality in the wife always included, in addition to physical examination and routine tests, vaginal smears, estimate of cervical pH, tubal patency and premenstrual endometrial biopsy study. Usually a basal metabolism test was done.

Testicular biopsy is adding materially to our knowledge of fertility. One useful purpose is that it relegates those cases not worthy of treatment to their proper category and is a splendid means of selecting

TABLE IX

	<i>Normal</i>	<i>Mildly Abnormal</i>	<i>Severely Abnormal</i>
Vol. cc.	2.0-6	10	0.5
Viscosity	slight	<	>++
pH	7.5-8.5	8.8	6.0
Count per cc. in millions	50-200	40	10
Total count in millions	250-1,000	100	50
Motility $\frac{1}{2}$ hour	4+ 80%	4+ 60%	4+ 10%
Motility 4 hours	4+ 70%	4+ 30%	4+ 0
Morphology normal	80%+	70%	40%
Other elements	Debris rare W.B.C.	Few W.B.C.	Many W.B.C. bacteria, R.B.C.

patients in whom it seems reasonable to use treatment. An excellent review of the subject is that of Charney¹⁰ of New York.

Widely varying pictures are presented. Some sections show developmental lesions, varying from those showing arrest of maturity at an early stage (Fig. 9) to those in which the appearance suggests lag in maturity plus tubular shrinkage and disappearance of spermatocytes with little to represent the tubules except Sertoli cells (Fig. 10). In some the basement membrane is extremely thickened and hyalinized.

Mumps' orchitis (Fig. 11) may produce mild to severe thickening of the basement membrane and mild to severe tubular damage reaching tubular hyalinization.

In some patients who are aspermic (Fig. 12), only a mild degree of disarrangement of the spermatogenic elements is seen. The development may reach to the spermatid stage and never mature beyond it. Even in such instances as these, the tubular damage may be sufficient to cause a distinct increase in urinary gonadotrophins.

In many cases where little or no abnormality is demonstrated, general advice as to rest, sexual habits, diet, strict moderation or avoidance of alcohol and tobacco, and the use of thyroid may be followed

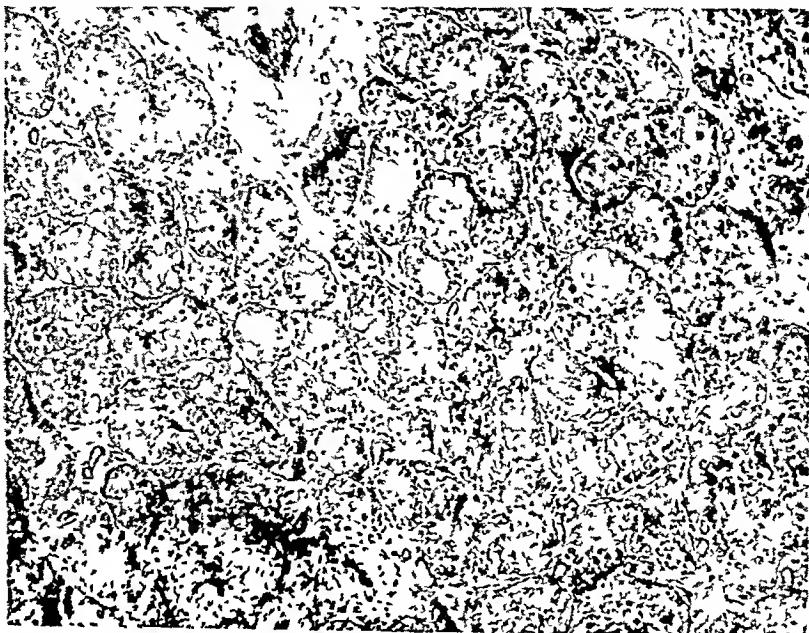


Figure 9 Testis biopsy from man age 20 Height 60½ inches Severe eunuchoidism Urinary gonadotrophins 6 m u /24 hrs Testis shows early developmental arrest

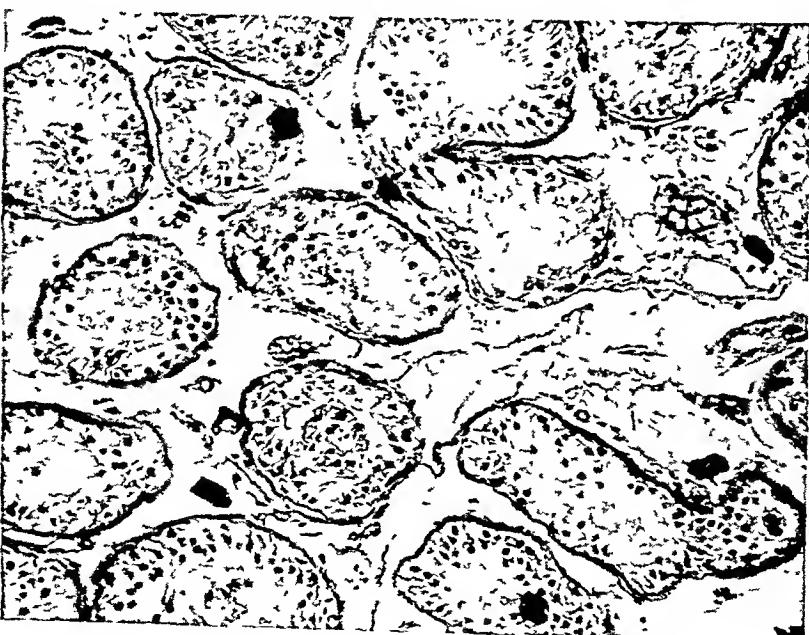


Figure 10 Testis biopsy from a patient classed as adiposogenital dystrophy—age 18 The tubules are comprised almost entirely of Sertoli cells The basement membrane is slightly thickened and the Leydig cells are less prominent than normal



Figure 11. Showing extreme testicular changes, the result of mumps' orchitis. Tubular change varies from tubules lined only with Sertoli cells to many which are completely sclerosed. There is apparent interstitial cell hyperplasia. Age 24.

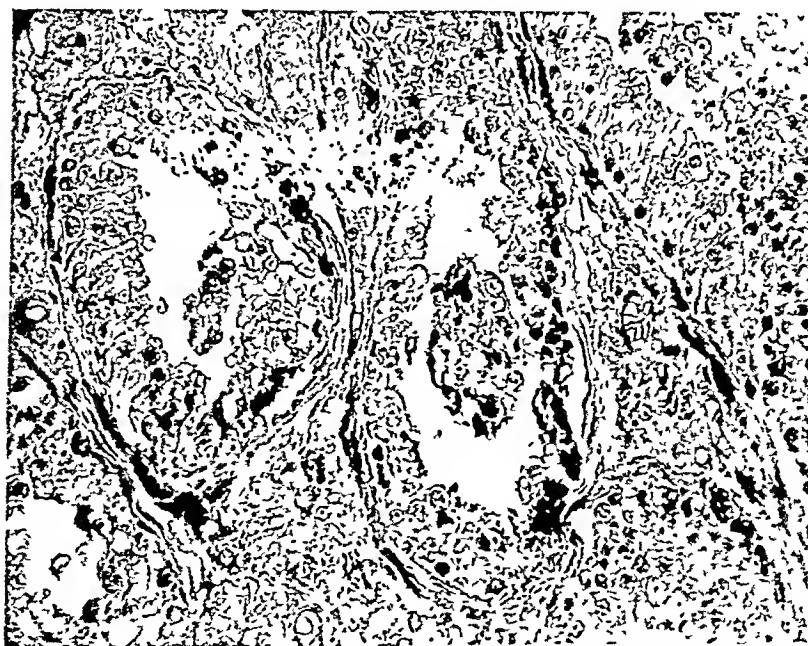


Figure 12. Showing relative mild degree of impairment of spermatogenic elements. Spermatids are present, no spermatozoa. Biopsy is from a man age 31, with azoospermia.

by pregnancy. In spite of the fact that there is good experimental evidence showing the intimate relationship of various vitamins, especially B complex and E, to spermatogenesis, their clinical value in the majority of patients is still questionable.

When the semen count is greatly reduced and testicular structure approaches normal, therapy with pituitary gonadotrophin should be tried. Unfortunately, much more frequently than not it fails. With steady improvement in therapeutic preparations and better selection of cases, better results may be anticipated. Testosterone and the recently recommended Δ^5 -pregnenolone have found no place as yet clinically in this problem. New methods of sperm concentration and artificial insemination, especially with the help of hyaluronidase, are being tried. In many instances in which the wife is normal, insemination from a donor seems the best solution, and if this is not desirable, adoption of a child should be advised rather than carrying on of treatment over an unreasonably long period of time.

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THE EFFECT OF IMMOBILIZATION ON METABOLIC AND PHYSIOLOGICAL FUNCTIONS OF NORMAL MEN*

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BEDED rest has been accused of contributing to or causing phlebothrombosis, pulmonary embolism, hypostatic pneumonia, decubitus ulcers, constipation, myasthenia, osteoporosis and nephrolithiasis. These are obviously serious charges against one of the most widely utilized forms of treatment in medicine. Not only is bed rest frequently condemned, it is also rarely defined. The term may be used to denote the inactivity of a comatose patient or the activity of a patient suffering with Graves' disease who is confined to bed. Our attitudes toward bed rest appear to be at once disparaging and confused.

Particularly because of the need for speeding the convalescence and rehabilitation of disabled soldiers in World War II, studies were devised to clarify the manner in which bed rest influences the physiological and metabolic derangements associated with traumatic and infectious states. Very few experiments have been carried out in which the effects of illness can be differentiated to any extent from those due to so-called bed rest. The purpose of our investigation¹ was to obtain quantitative metabolic and physiological data on the effects of bed rest on normal, healthy individuals. Such data would furnish a basis for differentiating the effects of bed rest *per se* from those which might arise from disease or trauma.

Our plan was to study human volunteers on the Metabolism Ward of the New York Hospital and the Russell Sage Institute of Pathology. The difficulty in such a human experiment is to keep as many factors

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** In collaboration with G. Donald Whedon, M.D., and Ephraim Shorr, M.D.

constant as possible. We did this as follows: The men were admitted to the ward and placed on constant diets which were calculated to maintain caloric, mineral and vitamin requirements. They were ambulatory, but exercise was standardized by allowing calisthenics, swimming and walking each day at definite times. The period of study of this phase of the experiment was called the control period and varied from six to eight weeks. Metabolic balance studies were carried on constantly as were physiological studies. During this period the men became adjusted to their new environment and their metabolic balances became stabilized on the diet.

The next phase of the experiment was called the bed rest or immobilization period. In order to define this and to standardize activity, we decided to place the men in bivalved plaster casts, extending from the toes to the umbilicus. This allowed movement of the arms and chest but little or no movement from the hips to the toes. This degree of immobilization might be found in such conditions as fracture of the spine or pelvis, poliomyelitis and hemiplegia. The men remained in the casts constantly except for use of the bed pan and during certain physiological tests. This bed rest or immobilization period varied from six to seven weeks.

During the third period, or recovery period, the men were taken out of the casts, became ambulatory on the sixth day and resumed their control level of activity at the end of two weeks. The recovery period varied from four to six weeks in duration. Four healthy men were studied varying from twenty to twenty-nine years of age.

In this paper we have summarized the results of a few of the metabolic and physiological studies.

Nitrogen metabolism: (Figure 1) During the control period all four men were in positive nitrogen balance; that is, they were storing small quantities of nitrogen. On going to bed, nitrogen excretion began to increase after the first four days and reached a maximum during the second week. Except for the delay, this is similar to the pattern of response which has been found in trauma or infections²⁻⁴ but is definitely less marked in extent than would be found in an acute illness. Three of the men developed negative nitrogen balances as evidenced by the fact that the nitrogen output exceeded the intake. Although subject C.O. did not develop a negative balance, his nitrogen excretion increased well above his control base-line (average of excretion during last four

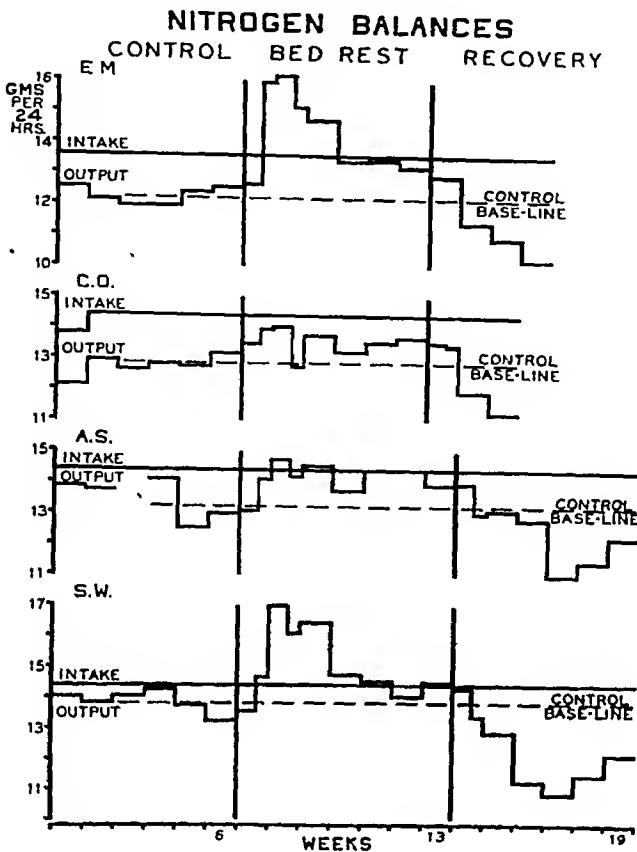


Figure 1. Effect of immobilization on the nitrogen metabolism of four normal male subjects. In this and in each of the subsequent graphs "bed rest" indicates the immobilization phase. For each subject the control baseline is an average of the total outputs of the last four control weeks. The nitrogen outputs of the first two weeks of immobilization and of the first recovery week have been charted in four- and three-day periods in order to indicate the duration of the delay in the increase in nitrogen excretion during immobilization, the peak of nitrogen excretion during immobilization, and the delay in the fall in nitrogen excretion during recovery.

control weeks). Practically all the nitrogen loss occurred in the urine. When the nitrogen losses of all four men were averaged and calculated on the basis of muscle protoplasm, it was found that the average loss per man was equal to four pounds of muscle. In the recovery period there was a steady fall in the nitrogen output until the fourth week with the result that the men were storing nitrogen in their bodies, then the output rose slowly and was just approaching the control level at the end of six weeks. Clinically, one would have said that the men were well and could be discharged from the hospital at the end of the third week,

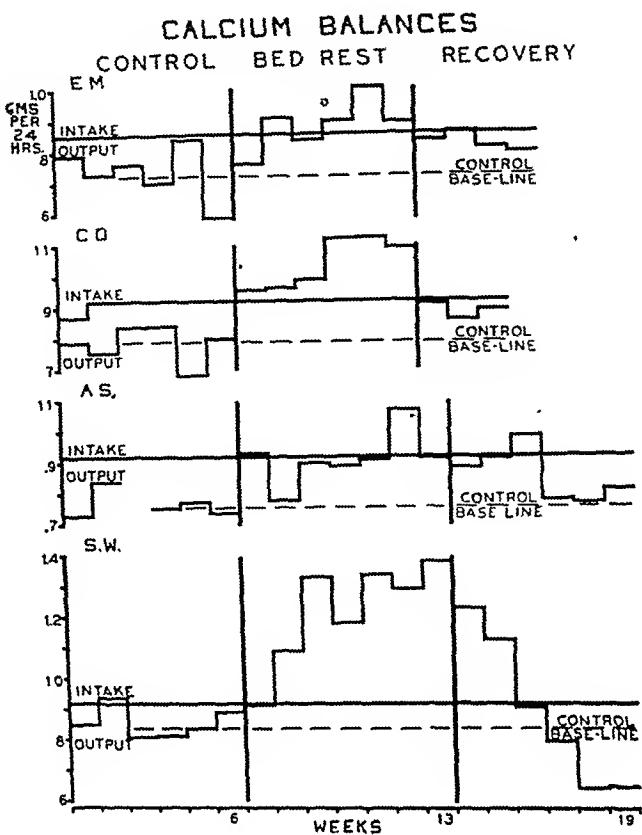


Figure 2. Effect of immobilization on the calcium metabolism of four normal male subjects.

but chemically (in terms of nitrogen metabolism) they had not quite recovered at the end of the sixth week.

Calcium metabolism: (Figure 2) Increased calcium excretion began at the time that the nitrogen output rose. It then increased steadily until the fifth week of immobilization. In all of the subjects the excretion of calcium in the urine more than doubled. Although there was variation from man to man, the total losses of calcium were more than half the values that have been found in fracture cases.⁵ In other words, immobilization in casts may account for half or more of the calcium loss during the treatment of a fracture. The average total (urinary plus fecal) calcium loss per man during six to seven weeks was 11 grams. The taller men lost more calcium than the men of shorter stature. In the first three weeks of the recovery period the excretion decreased slowly but still exceeded the control levels. Thereafter, calcium retention

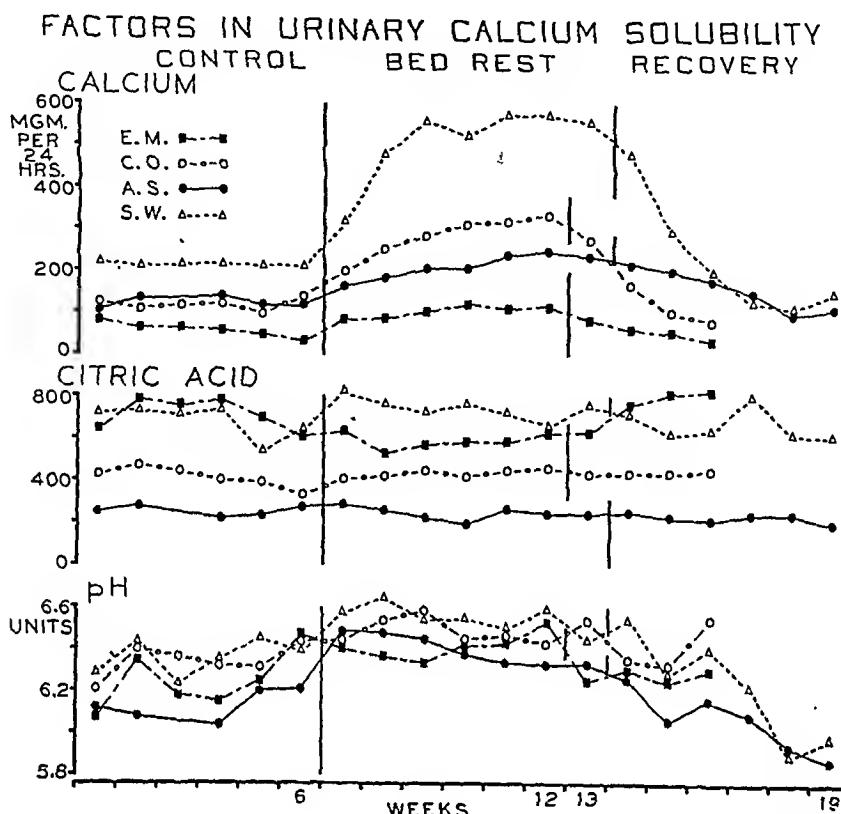


Figure 3. Effect of immobilization on the urinary excretion of calcium and citric acid and on urinary pH in four normal male subjects. Daily calcium intake was 0.852 Gm. for subject E.M., 0.920 Gm. for subjects C.O., A.S., and S.W.

occurred and continued for several weeks. The calcium excretion of S.W. had not returned to the control level at the end of the sixth week. Calcium appeared to be restored to the body at a slower rate than nitrogen.

The extensive outpouring of calcium in the urine raises the problem of urinary tract stone formation. Among the factors that influence the solubility of urinary calcium are the urine volume, urinary pH, and urinary citric acid.⁶ If the urine is acid and contains adequate quantities of citric acid it can hold a large amount of calcium phosphate in solution. These factors affecting solubility of calcium were studied in each subject.

Figure 3 demonstrates that in spite of definite increases in the urinary calcium, there were no corresponding increases in citric acid excretion

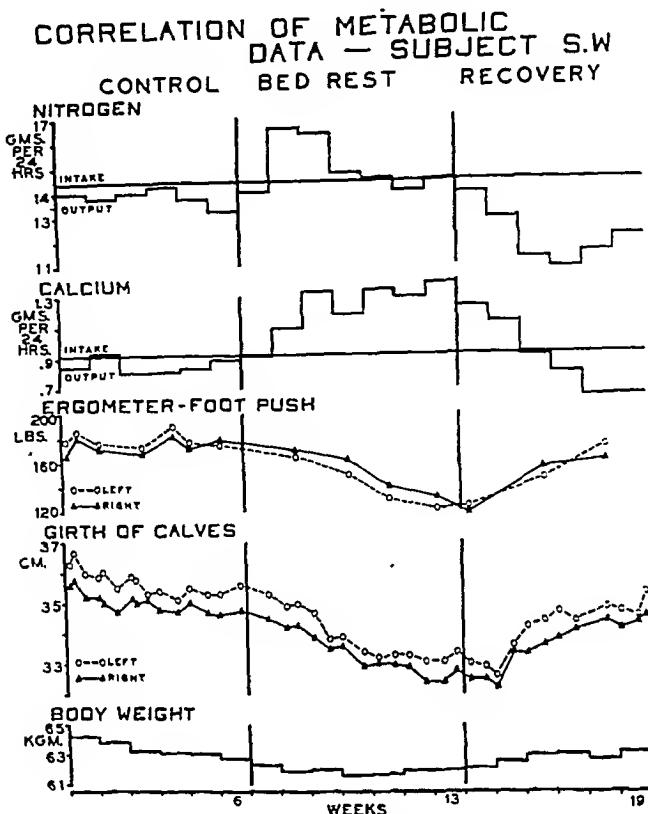


Figure 4. Effect of immobilization on nitrogen and calcium metabolism, gastrocnemius-soleus muscle strength, girth of calves, and body weight in subject S.W.

and the pH of the urine became slightly more alkaline. The urinary volume is not shown on the graph, but it increased only 200 cc. per day during the immobilization period. Thus, conditions were favorable for the formation of urinary calculi. Had dehydration or urinary tract infection occurred this hazard would have been accentuated. X-rays were taken of the kidneys and frequent examinations of the urine made, but no evidence of renal stone was found in any of the subjects.

An effort was made to correlate the nitrogen and calcium losses with the strength of the calf muscles as measured by the foot push on an ergometer, the girth of the calves and the body weight. The data as presented in Figure 4 for one subject suggest that the chief source of nitrogen and calcium loss was the immobilized legs in which the girth and muscle strength decreased as the excretion of calcium and nitrogen

increased. Two subjects lost weight and two of the subjects gained weight during immobilization. These weight changes were relatively small, and we have evidence to indicate that this was probably the result of simultaneous loss of muscle protoplasm and storage of fat or carbohydrate. In the recovery period the strength of the legs and the girth of the calves returned to the control period level at the end of the fifth week of recovery but calcium and nitrogen excretion were not back to the control level at the end of six weeks.

CIRCULATION

It is well known that patients may feel weak and dizzy on first getting out of bed after an illness. A tilt table was used as a method for determining the effect of bed rest on the circulation. The test was carried out by placing the subject on the tilt table in a horizontal position for a period of twenty to thirty minutes or until the pulse rate and blood pressure became constant. The tilt table was then tilted to 65° foot down and the subject stood motionless on a foot-board in this position. He was allowed to stand thus for twenty minutes unless he fainted in a shorter period. Pulse and blood pressure readings were made every one to two minutes. During immobilization the subjects were taken out of their casts thirty minutes prior to the test.

A fall in the pulse pressure was found to be the most important factor denoting a failing circulation in response to tilting. When the pulse pressure was reduced to between 10 and 12 mm. of mercury, a critical level was reached at which circulation became impaired, dizziness and pallor appeared, and fainting followed shortly thereafter.

After one week of immobilization in bed there developed an increasing tendency to faint when the subject was placed on the tilt table in the upright position, and critical pulse pressure levels were reached in a shorter period of time. This loss of circulatory control in the upright position became more marked as bed rest continued. Toward the end of the immobilization period all four subjects developed small purpuric hemorrhages about the feet and ankles at the end of the tests. The blood platelets, coagulation time of the blood, capillary fragility in the arms and the prothrombin times were all normal.

One subject afforded an unusual opportunity for studying the probable site of the defect which led to this loss of control of the circulation. During immobilization, this man fainted consistently after

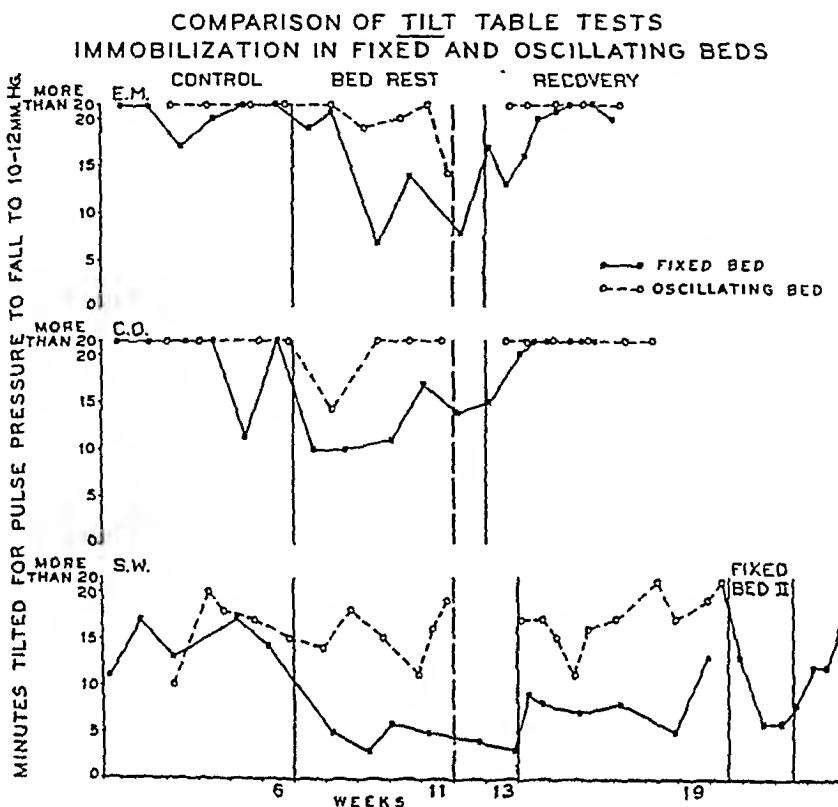


Figure 5. Comparison of the effect of immobilization in fixed and oscillating beds on the results of tilt table tests, showing the number of minutes in the tilted position (65 degrees feet downward) required for the pulse pressure to fall to critical levels of 10-12 mm. of Hg, three normal male subjects. The interrupted vertical line in the "bed rest" area of the graph marks the end of the five weeks during which the subjects were immobilized in oscillating beds; this convention has been adopted in this and in the following graph in order to permit comparison of physiological and metabolic changes during an equal period of immobilization, the immobilization phase of the fixed bed experiment having been six weeks in duration for subjects E.M. and C.O. and seven weeks for subject S.W. "Fixed Bed II" refers to a two week period of immobilization of subject S.W. in a fixed bed following recovery from immobilization in an oscillating bed.

six to eight minutes of standing on the tilt table. In order to determine if blood were trapped in the viscera, we bound his entire abdomen tightly with Ace bandages before tilting him in one experiment; he fainted as usual in eight minutes. The next day both legs were wrapped to the groin with Ace bandages and he did not faint in twenty minutes. The following day in the routine experiment without bandages he fainted in six minutes. The next day we again used bandages on the legs and he stood twenty minutes without fainting. It seemed obvious

that by increasing the support of the leg veins and capillaries we could prevent fainting and that the chief defect resided in the blood vessels of the immobilized legs.

Having found these disturbances in the circulatory apparatus and in metabolism that have been described, methods were considered by which they might be modified or prevented. The results of the tilt table tests gave a lead. If the position in bed could be altered frequently, one might avoid the circulatory disturbances and perhaps affect the metabolic derangements. Oscillating beds,⁷ used in the treatment of peripheral vascular disease, were available in the hospital. These beds are electrically driven to tilt back and forth on their long axis and can be adjusted to tilt the feet or head down. They require no extra nursing care and change the subject's position in bed at regular intervals. Three of the original volunteers were persuaded to return for an immobilization experiment⁸ using these beds instead of ordinary hospital or fixed beds. All factors were exactly the same as in the original experiment including identical diets except that the men were placed in their casts on the oscillating bed during the immobilization phase. The bed was run for eight to twenty hours each day, rocking from the horizontal to 23° foot down and return to the horizontal position every one and one-half minutes. The movement was so slow that the men often forgot that they were in motion and could sleep without difficulty during oscillation. The duration of the immobilization phase in the oscillating bed experiment was five weeks.

Figure 5 presents a comparison of the results of tilt table tests performed on three of the subjects during the fixed bed and oscillating bed experiments, showing the number of minutes in the tilted position required for the subject's pulse pressure to fall to critical levels. This graph demonstrates that in the fixed bed experiment during immobilization all three subjects reached critical pulse pressure levels on the tilt table in a much shorter period of time than they did during the control period. There was a marked difference in the reaction of the circulation during immobilization between the fixed and oscillating bed experiments. During immobilization in the oscillating bed, circulation was well maintained and showed only slight impairment; purpura of the feet did not occur although the men could and did stand for much longer periods of time on the tilt table than they could during the immobilization phase of the fixed bed experiment. These observations were checked by placing

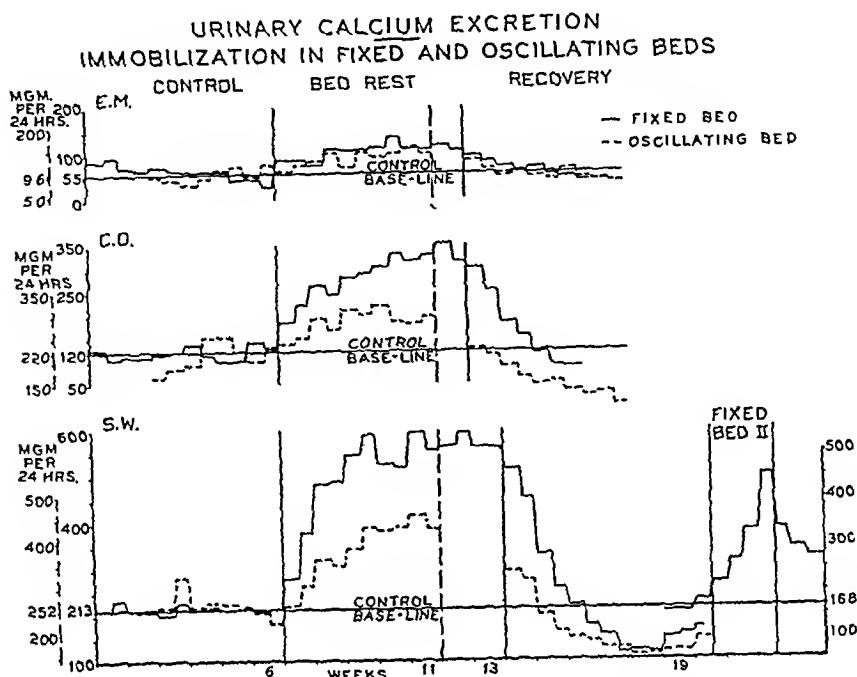


Figure 6. Comparison of the changes in the urinary excretion of calcium resulting from immobilization in fixed and oscillating beds, three normal male subjects. The ordinate scales for urinary calcium excretion (in Mgm. per 24 hours) have been placed so that the control base-lines of the fixed and oscillating bed experiments are superimposed. The control base-line urinary calcium excretion for the fixed bed experiment is an average of the outputs of the last four control weeks; for the oscillating bed experiment an average of the outputs of the last three control weeks; for the re-immobilization of subject S.W. in a fixed bed (Fixed Bed II) the control base-line is an average of the last two periods (eleven days) of the oscillating bed experiment recovery phase.

S.W. in his cast in a fixed bed after he had recovered from immobilization in the oscillating bed. When he was tested on the tilt table after seven days in bed, his pulse pressure fell to critical levels within six minutes, i.e., in just as brief a time as it had in his original immobilization in a fixed bed.

The effect of the oscillating bed on urinary calcium excretion is shown in Figure 6. E. M., who lost the smallest amounts of calcium in the urine during immobilization in the fixed bed, definitely lost even less in the oscillating bed. C. O. and S. W. lost less than half as much calcium in the oscillating bed as they had in the fixed bed. As a check on these observations, S. W. after six weeks of recovery from immobilization in the oscillating bed, was again placed in his cast in a fixed bed

for two weeks (as related above). He duplicated almost exactly the loss of calcium which he had demonstrated during the first two weeks immobilization in the original fixed bed experiment.

In simple terms, the oscillating bed acts in several ways. The degree to which the feet were dropped with each oscillation brought about some weight bearing on the heels and joints and probably caused slight muscle contraction. The venous pressure in one of the dorsal veins of the foot was measured and was found to change 140 mm. of water with each oscillation. Thus, there was very little opportunity for venous stagnation. When getting out of their casts at the end of bed rest, the subjects all stated that they had less weakness and joint stiffness than had been noted after the fixed bed experiment.

Many of the ill effects attributed to bed rest were not found in this study. Constipation did not occur and laxatives were not required by any of the subjects, although they were immobilized to a degree which is uncommon in the average hospital patient. Sedation was rarely used except during the first one or two nights in the cast. There may be no connection between sedatives and constipation, but it would seem wise to scrutinize some of our other methods of therapy as possible causes of constipation. The vital capacity and the maximum ventilation capacities were unaffected by bed rest. The basal metabolic rate fell only 7 per cent as averaged for the four men. The speed of the circulation at rest as measured from the arm to tongue and the coagulability of the blood were unaltered by bed rest. The circulating blood volume decreased on an average only 275 cc., or 5.4 per cent.

In condemnation of bed rest as defined in this experiment, it did cause a definite decrease in the size and strength of the legs. There was a definite loss of nitrogen from the body which reached its maximum during the second week and which we believe was probably due chiefly to the muscle atrophy of the legs. Calcium loss from the body increased slowly and became marked at the fifth week carrying with it a definite hazard of urinary tract stone formation. The control of the blood vessels of the legs was impaired and this became marked after two weeks in bed. The men complained rather bitterly of stiffness of the knee and ankle joints after the fixed bed experiment and this persisted in two of the men for several weeks after being discharged from the hospital.

In an attempt to modify these ill effects of immobilization, movement, such as is provided by an oscillating bed, may be of considerable

value. Use of this bed almost completely prevented the loss of circulatory control in the upright position which occurred in the fixed bed. It reduced the calcium loss by approximately 50 per cent and thus may be important in preventing urinary tract stone formation. The oscillating bed also reduced slightly the nitrogen loss. A patient's discomfort on being mobilized may be lessened by the use of such a bed; subjectively our subjects did not feel as weak and complained very little of joint discomfort at the end of immobilization in the oscillating bed experiment.

As a final interpretation of our results, it seems reasonable to state that during the first ten days of immobilization, as has been defined in this discussion, there was little evidence for physiological and metabolic damage to the human body. After two to three weeks, however, rather serious effects became manifest and must be considered as important problems in the management of patients with paralysis, fractures and long continued illness in which movement in bed is limited.

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THE CLINICAL SIGNIFICANCE OF NUTRITIONAL DEFICIENCIES IN PREGNANCY*

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FOR too long a time pregnancy has been considered a normal physiological function occupying a nine months interim at some time or times during a patient's child-bearing years. Fortunately, present day concepts of nutrition have shed new light, making possible a different interpretation, on what should be considered normal physiology. Undoubtedly, pregnancy should be a normal physiological function in the human female, but we rarely see a patient whose physiological response to pregnancy can be considered normal. It would then appear that our base line of normal has been established against patients who are sub-normal to begin with. For years, our attention has been concerned with the various catastrophes of pregnancy *after* these catastrophes have occurred, yet these observations have shed little light on the underlying causative or preventive factors.

Consequently, in 1935, we undertook to evaluate by clinical observations, the effect of improved nutrition on maternal and infant well-being. Our initial efforts were directed toward establishing a minimum optimum diet for pregnancy, one which would, of course, provide an adequate caloric value, estimated on the basis of the patient's weight at the beginning of pregnancy and her energy requirements. But of greater importance, one which would supply necessary amounts of animal and non-animal protein, carbohydrates and fats, and at least minimal protective amounts of the known vitamins and minerals. Since the average weight at the beginning of pregnancy, among the patients registered in the Prenatal Clinic at the Philadelphia Lying-in Hospital, was found to be 129 pounds, our standardized diet was arbitrarily established on this weight basis. It contains approximately 2200 calories, consisting of 110 grams of protein (of which approximately 80 grams

* Read April 1, 1947, at the Institute on Public Health of The New York Academy of Medicine.

are animal protein), 85 grams of fat and approximately 300 grams of carbohydrates. Every effort has been made to maintain a practical and palatable diet—one which a patient could be expected to eat. A theoretically ideal diet might be considerably different from one which is practical and optimum.

The success which we have had with improved nutrition in our research group of patients has been dependent upon several factors, among which are:

The patients attending the Research Clinic have been given intensive and persistent dietary instructions, both written and oral. It should be emphasized that this is primarily the physician's responsibility, and that only by individual dietary analysis, investigation of the patient's dietary habits and the specific correction of the dietary errors noted, can adequate results be obtained. The simple expedient of giving the patient a printed dietary outline, or telling her to eat a "well-balanced" diet, is ridiculous on the face of it.

Six small meals a day, at approximately three-hour intervals, have been found to be essential; and we have found a marked improvement will result in all patients if this regimen of interval feeding is adhered to. Such a regimen has been found to decrease markedly the severity of nausea and vomiting during early pregnancy, and to aid in the elimination of fatigue and other symptoms associated with energy depletion. The gastro-intestinal tract becomes hypotonic surprisingly early in pregnancy, and unless adequate measures are instituted immediately, this dysfunction will continue or become exaggerated and will result in a failure of intestinal absorption with resulting maternal and fetal shortages. It further aids in decreasing the intake of a high caloric carbohydrate diet by maintaining an active appetite which can be readily satisfied with the essential food elements without the uncontrollable desire on the part of many patients to substitute restricted items for required items of food.

There are excessive metabolic demands of pregnancy during the first trimester, or formative period of the fetus, and particularly during the third trimester, the period of most rapid growth and development. This makes it essential that there be an adequate caloric intake, and that it include sufficient energy producing and tissue protective foods to answer the patient's increased nutritional and metabolic requirements.

It has been stated that patients will not coöperate on such a regime.

We have not found this to be the case. Granted, it required persistent personal supervision and instructions to accomplish, but a most satisfactory response can be obtained once the interval regime has been established, except for those isolated patients who are unable to understand, who cannot for some vague reason conform, or those few who refuse to coöperate. We have yet to have a patient who has not frankly admitted an improvement in her general well-being after being on this schedule for a short time.

It should be noted that fruit and fruit juices have been restricted to two servings daily. Excessive ingestion of fruit and fruit juices, entailing intake of large amounts of fluid and sugar, has been found to be one of the more important dietary errors associated with the initiation of excessive gain in weight and edema, since in the majority of cases, the correction of this one dietary error aided materially in the elimination of these problems. Excess gain in weight and resulting edema usually do not result solely from the excessive ingestion of fruit and fruit juices, but because the patient takes these foods instead of adequate amounts of protein, thus materially increasing her caloric intake plus upsetting her protein-carbohydrate ratio. This error usually begins early in pregnancy, and initiates or furthers, a state of hypoproteinemia which we believe to be one of the primary causes of edema associated with pregnancy. It should be stressed that constant effort must be directed toward establishing an adequate intake of protein and that essentially pure carbohydrate foods are to be taken in addition to or after, not instead of, the essential foods necessary to the maintenance of normal physiology and metabolism.

Fluids have been restricted to a level of normal fluid balance, aiding materially in avoiding the tendency on the part of many patients to substitute fluids for adequate food. We believe that excessive retention of fluid can better be controlled by proper intake of food, rather than through excessive restriction of fluid or dehydrating measures.

We instruct our patients to restrict their total fluid intake to eight glasses a day. This has frequently been questioned as being an inadequate amount of fluid. Anyone who will take the time to observe and investigate the normal fluid balance level of a large group of patients, will find that patients in optimum physiological balance will be completely satisfied at this level, and will not show evidence of fluid retention. We have yet to see a patient with persistent edema whose fluid

intake did not exceed this level by at least 50 per cent or more. It has been our experience that fluid intake above the 64-ounce level is not at any time necessary. No doubt, many patients can stabilize on a fluid intake in excess of this, but for practical working purposes, experience has shown this to be an advisable level for an arbitrary base line. Obviously, all patients are not alike, and again individualization of each patient's requirements must be established.

It has been our experience that the majority of patients who show evidence of excessive fluid or fruit intake, have been substituting fluid or fruit for proper food. We believe that this has often resulted from errors in instruction by those responsible for nutritional advice, who do not realize that this is one situation where fruit is not a panacea.

Except where excessive salt intake is demonstrated, the restriction of salt has been found unnecessary. The primary object of this program is to obtain the patient's coöperation in eating correctly. As a diet with a moderate amount of salt is more palatable, the patient is more likely to follow instructions than were she advised to eat a salt-free diet. Since it is almost impossible to produce a diet with less than approximately 2.5 grams of salt and still retain palatability, a diet with less than this level is not considered feasible, or desirable. In individual instances in which toxemia has developed with evidence of edema, the problem immediately becomes one of major disturbance and must be individualized on the basis of the entire clinical picture, rather than the simple expedient of salt restriction. Among patients under positive nutritional control, this has not been a problem.

Our instructions to patients to refrain from eating pastry, ice-cream, candy and nuts, have been questioned as being a ridiculous request to make of any woman during pregnancy. In working with large groups of patients certain standards must be established, and it has been found that the above advice is essential, and except in isolated cases, has not produced any hardship or lack of coöperation on the part of our patients once the reason for this restriction is understood. Patients who are coöperating and are satisfactorily stabilized, are permitted occasional small amounts of the restricted items, but they are carefully instructed that these, as well as many other items of food, may be taken only after all other essential nutrients have been taken, never instead of. We have not found this to be a problem, and a majority of our patients have voluntarily stated that after being on the advised dietary, they

no longer have a great desire for ice cream, pastries and sweets.

The caloric requirements during pregnancy can not be arbitrarily stated for all patients. As stated above, we have established our specific dietary instructions on the basis of a beginning pregnancy weight of 129 pounds which we have found to be average. Obviously, patients weighing 90 pounds or 175 pounds at the beginning of pregnancy will require an entirely different caloric intake to maintain optimum gain in weight during their pregnancy. To answer the necessary energy requirements, diets containing 1600 calories or less, which have appeared in the literature from time to time, cannot possibly supply optimum or essential nutrients; and diets containing 3,000 or more calories are in excess of the caloric requirements for the average patient.

To repeat—the simple expedient of handing the patient a printed dietary outline is of no value in a long range nutritional program. Few, if any, patients understand the real reason for nutritional reinforcements during pregnancy, and they are entitled to complete and detailed individualized dietary instructions from their doctor.

The degree of nutritional adequacy at the beginning of pregnancy will determine the degree of deficiency which can be expected to develop should dietary habits remain unchanged. In other words, a patient whose nutrition is adequate at the beginning of pregnancy, and who maintains an adequate dietary regime, is better able to withstand the depleting effects of early nausea and vomiting and the increasing metabolic demands of late pregnancy without marked disturbance. On the other hand, the patient who begins her pregnancy showing definite signs and/or symptoms of deficiency, and whose nutritional intake continues to be inadequate, will show increasing degrees of distress, depending on the severity and velocity of the nutritional inadequacy. Our observations support the idea that the fetus obtains its nutritional requirements prior to the maternal organism, and draws upon maternal storages. When these storages are depleted to a point of deficiency in the mother, the baby will fail to obtain the necessary elements.

Some statistics showing the results of improved maternal and fetal nutrition illustrate the clinical significance of nutritional deficiencies in pregnancy. The results for the patients in the Research Group may be compared with those of the Control Group in that emergency admissions and others who had not registered for care in advance and had not made two or more prenatal visits have been excluded. All non-viable

TABLE I: STATISTICAL DATA

	<i>Research Group (593)</i>	<i>No.</i>	<i>%</i>	<i>Control Group (772)</i>	<i>No.</i>	<i>%</i>	<i>% Increase</i>
Total Baby Deaths		11	1.85		18	2.33	26
Stillbirths		5	0.84		9	1.16	38
Neonatal Deaths		6	1.01		9	1.16	15
Prematurity		24	4.16		54	7.07	70
Pre-Eclampsia		0	0		12	1.56	—
Eclampsia		0	0		1	0.13	—

1. Total baby deaths were 18 in the control group and 11 in the research group, or an increased incidence of 26 per cent in the Control Group over the Research Group.
2. In the Research Group, there were only five stillbirths and six neonatal deaths or 0.84 per cent and 1.01 per cent respectively. Among the 772 control patients, there were nine stillbirths and nine neonatal deaths, or 1.16 per cent and 1.16 per cent respectively, which represents an increased incidence in the Control Group of 38 per cent for stillbirths and 15 per cent for neonatal deaths.
3. Pre-eclampsia and eclampsia did not occur in the Research Group, where in the Control Group, there was an incidence of 12 cases or 1.56 per cent of pre-eclampsia and 1 case or 0.13 per cent of eclampsia.
4. There were 54 prematures in the Control Group and 24 in the Research Group, or an increased incidence of 70 per cent in the Control Group.

TABLE II: INCIDENCE OF OBJECTIVE AND SUBJECTIVE OBSERVATIONS

		<i>No. of Patients</i>	<i>% of Patients</i>
Total		165	100.0
Glossitis		162	98.2
Gums		136	82.4
Cheilosis		5	3.0
Stomatitis		5	3.0
Fatigue		115	69.7
Legs, Weakness, Pain		90	54.5
Gastro-Intestinal Hypotonia		85	51.5
Weakness		74	44.8
Anorexia		73	44.2
Constipation		61	37.0
Dyspnea & Palpitation		60	36.4
Irritability		53	32.1
Arms & Hands, Weakness, Pain		33	20.0
Burning of Feet		32	19.4
Insomnia		28	17.0
Muscular Weakness		19	11.5

infant deaths as well as all colored patients have also been excluded from both groups.

Data for the control group have been compiled from the year 1939, a period about the middle of the years included in the study.

VITAMIN DEFICIENCIES

We have been able to demonstrate signs and/or symptoms of nutritional deficiency, usually of the sub-clinical type, in at least 98 per cent of our patients.

Table II shows incidence of objective and subjective observations suggestive of nutritional deficiencies as found in patients of the present Nutrition Research Clinic.

Although nutritional deficiency of an advanced degree is comparatively uncommon in the Philadelphia area, sub-clinical states are by no means infrequent. The incidence of glossitis in 98 per cent of our patients and polyneuritis in at least 54 per cent clearly indicates the frequency of deficiency states of minor degree. The most commonly observed nutritional deficiency states are characterized clinically by evidence of vitamin deficiencies. The relationship between avitaminosis and the metabolism of other vital elements is not completely understood, except that for optimal metabolism adequate amounts of all essential food elements are necessary.

We have observed an incidence of sub-clinical scurvy in approximately 82 per cent of our patients. The gingivitis so commonly seen in pregnancy is usually attributed to an infection. It is true that infection is frequently present, but generally the underlying cause of the disturbance is a lack of Vitamin C.

Our observations show a much greater incidence of Vitamin A deficiency than has heretofore been suggested. Straumfjord states that vernix caseosa is a manifestation of deficiency of Vitamin A. This, together with other reported evidences, points to the fact that a high percentage of patients are lacking in adequate amounts of this factor.

The necessity for adequate amounts of the B-complex for satisfactory metabolism of protein and carbohydrates is well established, and the majority of the clinical observations of deficiency are characterized by evidence of a lack of these important vitamins.

Pregnancy demonstrates more readily than almost any other condition the fact that adequate intake of food in no way guarantees

optimum absorption, utilization or storage; yet it must be emphasized that it is essential to obtain the necessary nutritional elements from natural food sources, rather than from supplemental therapy alone.

The importance of vitamin supplementation is becoming more and more apparent as our clinical experience progresses, and further, such experience indicates that this supplementation should consist of a relatively high potency polyvitamin concentrate. Many workers have stated that the requirements for such factors as thiamin chloride, riboflavin, niacin and ascorbic acid are relatively low. Our observations clearly indicate that during pregnancy, the requirements for the known vitamins are comparatively high. This is especially true of the B-complex factors.

Throughout this study it has been observed that in many cases, a typical syndrome developed during the middle or latter part of the second trimester. This syndrome is characterized by fatigue, lassitude, mild depression and general physiological hypotonia. Frequently, this has appeared in patients known to be coöperating with our nutrition advice. With the advent of parenteral B-complex, patients of this type have made a prompt and satisfactory response to therapy, where previously they responded poorly if at all. This strongly suggests that even these apparently well stabilized individuals may fail to adequately absorb or utilize a well planned and optimum diet. It further demonstrates that in many cases there is an absolute necessity for parenteral polyvitamin supplementation, in order to by-pass the oral route, to re-establish normal intestinal absorption and efficiency. The indication is that the primary breakdown responsible for the development of disturbances occurring in late pregnancy, is usually initiated by an absorptive failure in the gastrointestinal tract, rather than a utilization failure. It should be emphasized that in pregnancy, parenteral vitamin therapy is essential in acute deficiency states, and may be necessary even in the mild chronic types, in order to obtain a satisfactory nutritional balance throughout the remainder of pregnancy.

We have not used supplemental calcium therapy in the research group of patients, and do not believe that calcium in its present available supplemental form is of any value in the prevention of dental caries, or as a substitute for calcium from natural food sources.

At present, the only reliable means by which a patient's nutritional status can be evaluated is by clinical observations. Technical studies are

TABLE III: HEMOGLOBIN VARIATIONS AMONG 688 PATIENTS AT THE TIME OF ADMISSION TO PRENATAL CLINIC, PHILADELPHIA LYING-IN HOSPITAL, JULY 23, 1947 TO AUGUST 18, 1947.

<i>Hemoglobin in gram</i>	<i>Number of Patients</i>	<i>% of Total Patients</i>
9.0 or less	14	2.0
9.5 " "	41	5.9
10.0 " "	81	11.7
10.5 " "	168	24.4
11.0 " "	285	41.4
11.5 " "	368	53.5
12.0 " "	456	66.3
12.5 " "	548	79.7
13.0 " "	610	88.7
13.5 " "	643	93.5
14.0 " "	672	97.7
14.5 " "	685	99.6
15.0 " "	687	99.9
15.5 " "	688	100.0

as yet unreliable for this purpose and are of value only in dietary analysis, or in determining the patient's actual food intake. In establishing the nutritional status of patients attending the Nutrition Research Clinic, the objective and subjective evidences suggestive of nutritional inadequacy are evaluated. These findings then become the base line against which therapeutic management is formulated.

ANEMIAS OF PREGNANCY

Our observations indicate that supplemental iron therapy alone is of little value, and that iron deficiency anemias occurring in pregnancy are rare. Most of the anemias being typically nutritional anemias, do not respond to iron alone unless accompanied by an adequate diet and supplemented with vitamin and whole liver therapy. Recent observations suggest a more prompt and marked response when iron was omitted and whole desiccated liver substituted.

The variations in hemoglobin level shown in Table III are of probable significance. The hemoglobin determinations were derived from all patients attending the prenatal clinic at the Philadelphia Lying-In Hospital from July 23rd, 1947, to August 18th, 1947, and were taken on the first day of admission and therefore can be said to represent the

hemoglobin in the individual patient at the time she became pregnant. A further sampling of hemoglobins, at repeated visits, among 175 research clinic patients has not shown a single incidence of blood dyscrasia, macrocytic or microcytic anemia. Since all of these anemias represent a normocytic anemia, it seems rational to assume that they are entirely of nutritional origin, and further supports the thesis of the significance of sub-clinical nutritional deficiency states occurring early in pregnancy or existing at the time pregnancy occurs.

If we were to accept suggested standards of 10 grams of hemoglobin as the low limit of normal for hemoglobin during pregnancy, it would be to accept a standard too far below a level commensurate with maternal and fetal safety, oxygen requirements and general physiological adequacy.

Considerable emphasis is at present being placed upon the need for folic acid with the inference that it is a cure-all for the true or simple hypochromic anemias of pregnancy. Folic acid has not been demonstrated as being effective except in the presence of true macrocytic anemias. Since macrocytic anemias are rare in pregnancy, in most areas, the indications for folic acid as a routine, and especially as an isolated therapeutic adjunct, are also rare. Again it must be emphasized that the anemias of pregnancy, except in the presence of blood dyscrasias, are the result of a nutritional deficiency; that adequate natural food dietary corrections must first be established, and that the proper supplementation can only be determined after proper evaluation of the type of deficiency existing in the individual patient being considered. It is believed that adequate amounts of folic acid to supply the needs of most patients will be available if the basic dietary is adequate, and that folic acid will be required only in cases of prolonged deficiency or severe acute states.

Unquestionably, the demands of the baby and the increased metabolic load of the mother create a markedly increased demand for the various vitamins. We have been unable to establish any standard dosage since it depends entirely upon the nutritional status of the patient at the beginning of her pregnancy, her dietary habits throughout pregnancy, and the period of pregnancy under consideration. Our efforts, therefore, have been directed toward improving the patient's nutrition through natural food sources, and supplementing her improved diet with sufficient dosage of the various vitamins to control the signs and/or

symptoms of the observed deficiencies and the estimated additional requirements of the developing fetus.

Repeated dietary surveys among large groups of comparable patients show a protein intake averaging about 55 grams per day, and since hemoglobin averages as shown in Table III are consistent with these findings, it is becoming more and more apparent that hemoglobin levels have a direct correlation with protein intake levels. It is well established that hypoproteinemia is a major factor in the production of hydremia. Since secondary, or simple, anemias of pregnancy are usually stated to be the result of a physiological hydremia, it is our opinion that the high incidence of the secondary anemias of pregnancy are the result of a hypoproteinemia, and the associated general under-nutrition. We do not believe that the so-called physiological hydremia of pregnancy is normal, but is in fact evidence of hypoproteinemia, and will increase as the intake of protein decreases, or requirements for protein increase. Therefore, our efforts are directed early in pregnancy toward a primary improvement in the patient's basic dietary, rather than the useless administration of iron, or hematopoietic stimulants without consideration of essential nutritional requirements.

TOXEMIAS OF PREGNANCY

We believe that the so-called toxemias of pregnancy are in reality a nutritional deficiency state. Since this condition constitutes one of the greatest hazards to the mother and baby, it has received a major portion of our attention. The fact that severe pre-eclampsia and eclampsia did not occur in the research group of patients, indicates these syndromes to be the result of a failure in maternal metabolism. This thesis is further supported by a marked decrease in the incidence of mild toxemia.

It is of considerable interest to us that in most patients with pre-eclampsia, the condition is readily reversible by means of nutritional therapy alone. This is particularly true if the onset of pre-eclampsia is recognized early and adequate nutritional therapy is immediately instituted. We believe the rate of gain in weight is the most important early clinical observation relative to the onset of pre-eclampsia. Patients adhering properly to our nutritional instructions, and maintaining a positive nutritional balance, have been found to maintain a weight curve characterized by either a plus or minus three pounds the first trimester.

Whether this is a plus or minus, ascending or descending curve, will be determined by the amount or severity of nausea and vomiting which occurs. The weight curve should rise one-half pound per week the second trimester, and one pound per week the third trimester, up to about the 37th or 38th week, at which time the weight usually remains constant, or slightly decreases.

During the second trimester, it is of critical significance if a patient gains two or three times as much as she should. For example, during the second trimester, the patient should gain two pounds per month, whereas many patients and doctors would attach little significance to a gain of four pounds during this period. However, this four pounds represents twice as much as the patient should have gained, and if this rate of gain is continued into the third trimester, no one would disagree that the patient's weight gain was in definite excess of optimum. Intensive efforts at nutritional stabilization should be instituted at any time during pregnancy that the gain in weight is excessive. Pre-eclampsia which has been allowed to continue even in a mild form, for a considerable period, will be found difficult to improve, and may even be irreversible. This strongly suggests a physiological breakdown in the patient's metabolic processes beyond a point commensurate with the comparative slowness of nutritional therapy instituted late in pregnancy. This further indicates the absolute necessity for early nutritional stabilization as a preventive measure, rather than waiting until after a catastrophe has occurred and then relying on emergency measures. We are adamant in our opinion that should personal instruction fail to produce immediate correction of early evidence of toxemia, the patient must be hospitalized, or in some other way made to re-establish an adequate nutritional status. We have found it to be more expedient to hospitalize our patients early for restabilization procedures of a preventive nature, than to wait until a severe catastrophe occurs which will require prolonged hospitalization, and not infrequently radical procedures to terminate the pregnancy.

PREMATURITY

The incidence of only 4.16 per cent of prematurities in the research group as contrasted with an incidence of 7.07 per cent in the control group, or an increased incidence of 70 per cent in the control group over the research group indicates the significance of adequate nutrition

in pregnancy particularly from the point of view of infant salvage. This same tendency towards increased birth weights above premature levels, occurring in conjunction with improved maternal nutrition has been verified by several other clinics.

INFANT MORTALITY

A decrease in stillbirths and neonatal deaths is undoubtedly effected by several factors in any clinic. However, an increased incidence in total infant mortality of 26 per cent in the control group, over the research group which had improved maternal nutrition, suggests that adequate amounts of nutritional elements have played a major part. Since the placenta is maternally nourished, it seems rational that many of the infant catastrophes can be ascribed to a nutritional failure in the placental bed; the result of an inadequate intake, or inability of the mother to supply the essential elements needed for placental storage and placental cellular function. Statistical data are not available as yet, but there is a definite indication that the infant salvage from stillbirths and neonatal deaths can be increased as our methods and techniques of maternal nutrition are improved.

Maternal nutrition is of equal or greater importance than any other service. That it can materially improve maternal and infant health, and provide for a reserve against the depleting effects occurring in pregnancy, seems obvious. Likewise, it should be most obvious that the betterment of the mother and infant, and the increasing of infant salvage, must commence not later than the beginning of pregnancy, rather than at some later date when it becomes apparent that the well-being of the newborn infant is substandard.

CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

APRIL 29, 1948

*The Changed Status of Diphtheria Immunity**PHILIP COHEN, HERMAN SCHNECK, EMANUEL DUBOW and
SIDNEY Q. COHLAN

Diphtheria is on the increase. For several years, the morbidity and mortality rates of this disease have been increasing in various sections of this and other countries. This changed situation presents a challenge to both physicians and public health authorities.

A survey of the literature reveals a surprisingly high percentage of Schick-positive tests in adults in this and other countries. This is a striking change from the 86 per cent adult immunity demonstrated by Schick's analysis of data in Vienna and New York, and Park and Zingher's studies of diphtheria immunity in New York as shown by the Schick test. The era of prophylactic immunization, which began thereafter, resulted in a tremendous decline in diphtheria morbidity and mortality, but was also accompanied by a similar decline in diphtheria carriers, with a consequent loss of the natural stimulus to immunity. Since Fraser and Brandon and others have shown that immunity after toxoid injections is effective for but three to five years, repeated injections at such intervals are necessary for the maintenance of effective immunity of the adult population to diphtheria. This indication of increased adult susceptibility to diphtheria may account for the increasing incidence of diphtheria outbreaks in various parts of the world.

At the Beth Israel Hospital a total of 683 Schick tests and controls were performed upon unselected women. Of this

total, 274 or 40.1 per cent were positive and 409 or 59.9 per cent were negative. Antitoxin titrations demonstrated that Schick-negative patients had .01 or more units of this antitoxin in their blood. The Schick-positive reactors had less than this amount of antitoxin in their blood with few exceptions. Previous childhood immunization seemed to have no influence upon the percentage of adults yielding a positive Schick test, for the percentage of those previously immunized was the same in both the Schick-positive and Schick-negative groups. This appears to indicate that childhood immunization has little effect on the immunity of an adult population, unless reinforced periodically until adult life.

It follows that it is now incorrect and unsafe to assume, as in the past, that almost all newborn infants are immune to diphtheria. Although newborn infants whose mothers were Schick-positive usually showed a negative reaction to the Schick test (anergy), they were nevertheless susceptible to diphtheria as was demonstrated by the fact that the antitoxin titer of their serum was less than .01 unit per cc.

The authors recommend, as the remedy, selective immunization of infants. Diphtheria prophylaxis is begun at two months of age if the maternal Schick test is positive, and at four months of age when the maternal Schick test is negative. At this age the diphtheria antitoxin transmitted to the baby usually disappears from the baby's

* From the Pediatric Service, Beth Israel Hospital, New York City. This work was aided by a grant from the Loyal League Philanthropies, Inc.

blood, permitting optimal antitoxin response to the toxoid. Three injections are given at monthly intervals—0.5cc., 1cc.—and 1cc.

Since the newborn is infrequently immune to pertussis and tetanus, combined immunization is indicated beginning at two months of age or four months of age, according to the immunological status of the mother. If the mother is Schick-negative, it may be advisable to begin pertussis immunization at

two months of age, and at four months combine further injections with diphtheria and tetanus, if the last is desired. Preparations of combined toxoids and pertussis bacilli vaccine of adequate dosage are now available—so that three injections at monthly intervals in dosage indicated for uncombined diphtheria toxoid will achieve adequate immunity against all these infections.

* * *

*Changes in Lysozyme Formation in the Human Colon in Various Emotional States**

WILLIAM J. GRACE, PAUL H. SETON, A.B., STEWART WOLF,
and HAROLD G. WOLFF

Lysozyme, a mucolytic enzyme was described by Fleming in 1922. Since then it has been found to occur in nasal mucus, tears, saliva and in gastric, duodenal, ileal and colon secretions. Meyer has demonstrated that the enzyme is present in unusually high concentration in the stools of patients with chronic ulcerative colitis and in relatively low concentration in non-ulcerative chronic diarrheas. Recently Meyer has produced acute ulcerative lesions of the upper gastrointestinal tract by feeding lysozyme to dogs. He postulates that lysozyme destroys the protective mucous coating of the intestine and exposes the unprotected

mucosa to the action of noxious agents or indigenous bacterial flora.

This study, designed to explore the circumstances under which variations in lysozyme concentration occur, includes the measurement of stool lysozyme in random and 24-hour specimens from patients with various types of bowel disorders as well as healthy persons and subjects with diseases other than those involving the colon primarily. All determinations were done by the viscometric method of Meyer.

Day-to-day determinations of stool lysozyme were done on the following subjects.

(I) A 26 year old male with ulcerative

Our findings are as follows:

Normal subjects	- - - - -	0.3—1.7 units per gram wet
Acute congestive heart failure	- - - - -	1.2 "
Cancer of the large intestine	- - - - -	3.2 "
Mucous colitis (mild cases)		
(a) Constipation	- - - - -	0.6—1.0 "
(b) Diarrhea	- - - - -	0.4—1.5 "
Chronic ulcerative colitis		
(a) In remission	- - - - -	0.7—1.6 "
(b) Mild symptoms	- - - - -	13—15 "
(c) Moderately severe	- - - - -	40—100 "
Regional enteritis (in remission)	- - - - -	0.4—0.8 "
Acute (24 hour) gastroenteritis	- - - - -	0.7 "

* From the Departments of Medicine and Psychiatry of the New York Hospital and Cornell University Medical College.

colitis of 6 years' duration. The patient has a loop of ascending colon on the surface of the abdominal wall. This segment of bowel had prolapsed through a colostomy wound. When the patient was calm, secure and relaxed the lysozyme concentration of the secretions of this loop was low (14-36 units per gram). When the patient was tense, irritated resentful and hostile the lysozyme values were much higher (57, 80, 100 units per gram).

(II) A 36 year old nurse with ulcerative colitis, control specimens on days of mental calm, security and relaxation revealed low values (0.4-2.5 units per gram). On a day following a distressing visit with her mother-in-law, and following a day of argumentation with her husband, both events being associated with considerable guilt, hostility and resentment, lysozyme concentration rose to 14 and 25 units per gram. During this time there were no changes in symptoms.

(III) A 32 year old physician, during times of relative security and relaxation showed lysozyme stool concentrations of low magnitude (0.4-0.6). Following the delivery of

a lecture, and following a migraine headache lysozyme concentration in the stool increased to 1.2 and 2.5 units per gram.

(IV) A 36 year old negro chorus girl in a situation which threatened to end her career developed mucous colitis. Lysozyme at this time was relatively high (27 units per gram). Following reassurance and moral support this finding decreased to 14 units. A subsequent episode associated with resentment and hostility brought a return of symptoms and a rise of lysozyme to 25. Later in a calm period lysozyme fell to 8 units.

(V) During the course of ulcerative colitis in a 32 year old female treated in the usual way without psychotherapy, lysozyme values remained essentially unchanged.

(VI) Pre- and post-operative vagotomy stool specimens were done on a 41 year old male with ulcerative colitis. For three days following the procedure lysozyme values rose to 44, from a preoperative level of 15. By the 5th postoperative day the values had returned to their former levels and have remained there.

* * *

*The Use of Para-Aminobenzoic Acid in Amebiasis: Preliminary Report**

KERMIT G. DWORK

A group of 12 patients with amebiasis was treated with the sodium salt of para-aminobenzoic acid (sodium paba). This study was undertaken purely on an empirical basis, but it was subsequently learned that Brackett and Bliznick¹ demonstrated marked amoebicidal activity of paba *in vitro*.

The patients were chosen at random from those not previously under the care of a physician. All but one of them recently emigrated from Porto Rico and are living on a relatively low socio-economic plane.

Diagnosis was based on the finding of *Endamoeba histolytica* in the stool. None

of the patients had evidence of involvement of the liver.

Treatment was conducted on an outpatient basis and the patients took the drug themselves during the day only. No paba blood levels were done.

The absorption and excretion of sodium paba is quite rapid, and it has been found necessary by a number of investigators to administer doses at two- and three-hour intervals to maintain a level in the therapeutic range of 30 to 60 milligrams per hundred cubic centimeters of blood. Therefore, any dosage schedule in which the drug is not

* From the Tropical Disease Diagnostic Service, Department of Health, New York City. Acknowledgement is due to Dr. Howard B. Shookhoff, Director of the Tropical Disease Diagnostic Service, for suggestions and advice. Sodium paba was furnished by the International Vitamin Corporation.

TABLE I

<i>Case Number</i>	<i>Patient</i>	<i>Age</i>	<i>Sex</i>	<i>Symptoms</i>	<i>Sodium Paba Treatment</i>	<i>Length of Follow-Up</i>	<i>Number of Negative Stools</i>	<i>Improvement in Symptoms</i>
1.	JP	21	M	None	2.0 q3h	7 days	*	
2.	NR	10	M	Pain, anorexia, fever	1.0 " "	"	*	✓
3.	WS	14	F	Pain, anorexia, gas, nausea	2.0 q4h	" "	*	✓
4.	AT	32	F	Pain, anorexia, gas	1.5 q2h	" "		
5.	DR	30	F	None	2.0 q2h	10 "	* ⁿ	✓
6.	IO	54	M	None	3.0 q2h	7 "	†	
7.	HM	10	M	Pain	1.5 q2h	" "	*	0
8.	FV	38	F	Pain, gas	2.0 q2h	" "	* ⁿ	✓
9.	OL	12	M	Diarrhea, vertigo, pain, fever	1.5 q2h	" "	4 wks.	C1W1 ✓
10.	AG	30	F	Pain, gas	2.0 q2h	12 "	30 wks.	C2W2 ✓
11.	AR	10	F	None	1.0 q3h	10 "	*	
12.	MH	28	F	Diarrhea	2.0 q2h	14 "	11 wks.	C1W6 ✓

* Stool positive for *E. histolytica* following treatment.

† Failed to return to clinic.

ⁿ Inadequate dosage.C Number of cold stools.
W Number of warm stools.

taken during the night results in the virtual absence of paba from the blood stream for at least 5 night-time hours. This condition obtains in the present study. Consequently, if encouraging results are obtainable under such conditions the effectiveness of the drug with hospital management and daily determinations of blood paba levels might well be markedly enhanced.

Out of the 12 cases studied, 2 complained of nausea or vomiting and stopped their medication within a short time (cases 5 and 8). One patient did not return after the first visit (case 6). These 3 cases are not included in the interpretation of results (Table I).

Repeated examination of the remaining 9 cases revealed that 4 had negative stools following treatment with sodium paba.

Attention is directed to case 12 (the only non-Porto Rican in this series) whose amebiasis had been refractory to standard carbarsonic therapy. Subsequent treatment with sodium paba resulted in the cessation of diarrhea and continued absence of amebae from the stools.

TABLE II

	<i>Dosage Interval</i>		
	<i>q4h</i>	<i>q3h</i>	<i>q2h</i>
Number of cases	—	1	3
Arrest	—	0	0
Failure	—	1	3

Further study of the dose frequency reveals evidence of the importance of giving medication frequently (Table II). Thus, of the 4 patients who were given sodium paba at intervals of 3 or 4 hours, none showed a therapeutic response. On the other hand, of the 5 patients who took the drug at two-hour intervals, 4 showed persistently negative stools following treatment. This increased response suggests the importance of maintaining an adequate blood paba level both by means of frequent dosage and by conducting treatment on a 24-hour basis.

Repeated examinations for a period of a

year will be necessary to determine whether cures are apparent or real.

Summary and conclusions:

1. Twelve patients with amebiasis were treated with sodium paba, the drug being omitted at night. It was possible to evaluate the results of treatment in 9 of the 12 cases.

2. Evidence of clinical and laboratory arrest of the disease followed administration of sodium paba in 4 of the 9 cases.

3. Of the 7 patients with symptoms, all

but 1 showed disappearance or improvement in symptoms following treatment.

4. Sodium paba gives promise of altering favorably the course of amebiasis. Further investigation with 24-hour treatment schedules and daily blood paba determinations is indicated.

REFERENCE

- Brackett, S. and Bliznick, A. The rate of multiplication of *Eudamoeba histolytica* and its relation to in vitro drug testing and possibly to nutritional studies. *J. Parasitol.* 1947, 33:154.

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*Studies on Cardiac Function: The Occurrence of Extrasystoles During Variation in the Emotional State in Man**

IAN P. STEVENSON, CHARLES H. DUNCAN and
STEWART WOLF

In view of a long standing impression among clinicians that the occurrence of cardiac arrhythmias is often related to emotional disturbances, it was considered of interest to carry out a systematic experimental study of this relationship. Seven patients were studied. Observations of attitude and feelings as well as general bodily reactions were made simultaneously with the recording of the electrocardiogram.

After an appropriate control period of re-

laxation and security during which no extrasystoles were recorded, an interview was begun in which topics involving significant conflicts were abruptly introduced. In each instance the very prompt recurrence of extrasystoles was recorded and in addition the subject displayed evidences of anxiety, resentment or depression. During relaxation until reassurance the extrasystoles were in each instance made to stop altogether.

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* * *

*The Relationship Between the Erythrocyte Concentration and the Specific Electro Conductivity of Blood**

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PH.D., CONSTANCE FREY, B.A., and IRVING S. WRIGHT

It has long been known that the erythrocyte constitutes an almost perfect non-conductor of electrical current in which characteristic it is almost unique among tissues. Stewart, Oker-Blom, Wilson and others

have utilized this characteristic to make possible the determination of the hematocrit and mean cell volume by electrical techniques.

This study is an attempt to utilize the

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non-conducting property of the red blood cell for the determination by electrical methods of the numbers of erythrocytes per unit volume of whole blood.

The specific conductivity of physiologic saline solutions containing various concentrations of washed red blood cells has been measured on an alternating current bridge and the results plotted against actual red blood cell counts of the samples using the standard technique.

The electrical circuit used employed a variable frequency oscillator which supplied an alternating current to a modified wheatstone bridge with an incorporated Wagner ground. A cathode ray tube was employed as the null indicator. Provision was also incorporated for the use of a cathode ray oscilloscope as a null indicator. The experiments were run at a frequency of 5000 cycles per minute since it was determined experimentally that minimal polarization effects were present under these circumstances. The conductivity cell was of a standard U type employing platinum electrodes.

The empirical results of these experiments revealed the probable existence of a mathematical relationship. This was evolved and appears to be:

$$g = C \times \frac{K_0 - K}{K_0 + K}$$

when

g = concentration of r.b.c. in millions per cu. millimeter.

C = a constant which has a value of 9.62×10^6 .

K_0 = the specific conductance of plasma.

K = the specific conductance of whole blood.

The accumulation of experimental data indicates that the formula is valid. By using it we have been able to make satisfactory red cell counts on both saline cell suspensions and heparinized whole blood samples with reasonable accuracy.

It has been found that patients with normocytic anemias have bloods of a higher specific conductivity than do normal people; it also has been shown that patients with polycythemia have blood of a lower specific conductivity than do normals. It has been possible to satisfactorily calculate the red blood cell count on these patients using the specific conductivity as the basis for calculation.

Work is at present in progress to design a satisfactory electronic circuit which will make possible red blood cell counts of a greater accuracy, and with less tedious work than is now possible using present techniques.*

* The opinions expressed are the personal ones of the authors and may not be construed as official, or as representing the views of the Navy Department as a whole.

This work has been aided by grants from the Eli Lilly Co., Sharp and Dohme Inc., the Albert and Mary Lasker Foundation and the Hyde Foundation through the New York Heart Association, and the U. S. Navy.

* * *

The Disappearance of Edema Through Diuresis Following Artificial Elevation of Plasma Sodium and Bicarbonate

CHARLES L. FOX, JR., D. J. McCUNE, A. H. BLAKEMORE,
R. E. MOLOSHOK and S. DE LANGE

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Edema, ascites and oliguria are usually associated with decreased plasma sodium and acidosis (Atchley, J.C.I., 1930, 9, 265). Extracellular water then migrates into cells (Peters, Phys. Rev., 1944, 24, 491; Gamble,

Extracellular Fluid, Boston, 1942), resulting in reduction in plasma volume (Darrow, J.C.I., 1935, 19, 419; Winkler, J.C.I., 1944, 28, 111). Impaired excretion of water follows (McCance, Proc. Roy. Soc. B. 1935-6,

119, 245). These abnormalities prevailed in one patient during anuria after diabetic acidosis; in one example of Chiari's syndrome after operation to produce portacaval shunt followed by numerous taps of the peritoneum and pleura; and in 14 patients with the nephrotic syndrome.

Correction of low plasma sodium and bicarbonate might be hoped to augment plasma volume and subsequently increase output of urine and chloride, thereby removing anasarca. Accordingly, sodium lactate and subsequently sodium and potassium acetate were administered orally. Initially body weight increased. Plasma sodiums rose from 120-135 mEq per liter to above normal; plasma bicarbonates from 9-20 mEq per liter to normal or above. Plasma volumes estimated from falling hematocrit expanded as much as 40 per cent. Daily clearances of

sodium, bicarbonate and endogenous creatinine increased several fold. Daily urine flow rose from 0.05 to over 4.0 cc. per minute as urine chloride concentration increased from 0.1 to 1.5 times the plasma value. Anasarca then disappeared.

In the balancee studies the recovery of sodium approximated that anticipated from the volume of edema fluid eliminated but the chloride jettisoned was in marked excess.

Although there are other procedures for the relief of anuria (artificial kidney, peritoneal lavage) the relative simplicity of correcting the biochemical and physiologic abnormalities in anuria suggests that this procedure receive more extensive trial. Likewise in the nephrotic syndrome, the results to date warrant further study of the significance of the electrolyte abnormalities.

* * *

*Evaluation of Pentaquine as a Cure of Relapsing Vivax Malaria**

A Controlled Study of Ninety-five Cases

BERNARD STRAUS and JOSEPH GENNIS

Investigations reported by the Board for the Coordination of Malaria Studies indicated that pentaquine (SN 13,276) 6-methoxy - 8 - (5-isopropylaminoanilino) - quinoline, when combined with quinine is effective in the eradication of relapsing *P. vivax* malaria.

The present investigation was designed to test the efficacy of pentaquine when combined with quinine in the definitive therapy of the naturally acquired *P. vivax* infection in man.

Methods: The patients studied were all veterans of World War II who were hospitalized at the Veterans Administration Hospital, Bronx, New York. Because of progressive development of immunity and the unpredictability of the relapse rate it was decided to employ a control series. Chloroquine (SN 7618), 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline,

was selected for the control series because it is a highly effective agent in the treatment of the immediate attack and has little, if any, effect on the relapse rate. Chloroquine diphosphate was administered in a dosage of 0.6 gm. of chloroquine base followed in six hours by 0.3 grams and 0.3 grams on the second and third days. Pentaquine was employed as the mono-phosphate in a daily dose of 30 mgms of pentaquine base, 10 mgms being given every 8 hours together with 0.6 grams of quinine sulphate. This regimen was maintained for 14 days. Pentaquine was given in one-half of the recommended daily dosage of 60 mgms of base in an attempt to reduce toxicity. This was feasible because there was reason to believe that some degree of immunity had been developed by most of the veterans who would undergo therapy.

Beginning in January 1947, alternate

* Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

cases were selected for either chloroquine or pentaquine therapy. All patients had proven vivax malaria.

There were 46 patients in the chloroquine series. Forty of these patients saw service in the Southwest Pacific area. There were 49 cases in the pentaquine group. Forty-four of these served in the Southwest Pacific area.

Follow up studies were made at approximately monthly intervals. The follow up study is still under way. The length of follow up varies from 1 week to 14 months. All patients will be followed for a minimum period of one year. Eighty-five per cent of the entire group have had a follow up period of more than 4 months at this time.

Results: None of the 49 cases in the pentaquine group has relapsed to date. In the chloroquine control group of 46 patients, there were relapses in 14 patients or 30 per cent. Twelve of these were from the Southwest Pacific. There were 18 relapses in the 14 patients. One patient had three relapses; two patients suffered two relapses; 11 patients have had one relapse. Four patients in the chloroquine group were subsequently treated in a relapse with pentaquine and are also included in the pentaquine series. All other chloroquine relapses were treated subsequently with chloroquine.

Toxicity: Toxic manifestations to penta-

quine-quinine were minor. In no case was it necessary to discontinue pentaquine because of toxicity. In one case it was necessary to discontinue quinine. Some toxic manifestations were observed in 75 per cent of patients. Most of these were insignificant. Nausea and anorexia were common during the first four days. Vomiting occasionally occurred during this period. Mild abdominal pain was relatively frequent after the first week. Tinnitus, dizziness and headache were not infrequent. No frank hemolytic reactions were observed, but 6 patients showed a drop of 1 million red blood cells or less per cu. mm. of blood in the course of therapy. Drug fever of 99.6-103.4 degrees developed in 7 patients, from the 7th to 11th day of therapy, and subsided spontaneously in one day. Many of the toxic manifestations probably were due to quinine.

Conclusion: In the treatment of relapsing *P. vivax* malaria of World War II veterans, pentaquine-quinine in the indicated dosage is apparently a highly effective curative agent. Toxic manifestations were insignificant at the dosage level employed. These results confirm the observations of Alving and of Coatney that even with one-half the previously recommended dosage of pentaquine, eradication of relapsing vivax malaria is achieved. Further follow-up is essential before a final evaluation can be made.

* * *

Differential Diagnosis of Diaphragmatic Hernia and Coronary Heart Disease

SIMON DACK, JACOB STONE, ARTHUR GRISHMAN, and
ARTHUR M. MASTER

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It has frequently been observed that patients with diaphragmatic hernia have pain in the lower part of the chest; in coronary artery disease, too, gastrointestinal symptoms are common. Thus the differential diagnosis of hiatus hernia and disease of the coronary artery is important. During the past twenty years, there has been a marked increase in the frequency of occurrence of

both conditions. On the basis of the physiological experiments of Dietrich and Schwieck and of Gilbert and Fenn, it has been assumed that diaphragmatic hernia produces constriction of the coronary artery reflexly through the vagus nerve, and that the two conditions are interdependent.

We are of the opinion that hiatus hernia can be distinguished from coronary artery

disease, and that when both conditions are present, the clinical significance of each can be properly evaluated. This report is based on a study of fifty consecutive patients with diaphragmatic hernia. The age range was between 40 and 60 years; a few were younger and some were older. About one-fourth had gastrointestinal complaints alone. A few presented only cardiovascular symptoms. Almost three-fourths of the patients had a combination of dyspepsia, dysphagia, and the like, and such symptoms as pain in the chest, palpitation of the heart, rapid heart rate.

To determine the existence of organic coronary disease, the following clinical examinations were done: teleoroentgenogram, roentgenoscopy, resting electrocardiograms, including Wilson unipolar precordial and extremity leads, the "2-step" exercise electrocardiograms and the 10 per cent anoxemia test. These were correlated with the history, operative findings, post-mortem findings, and clinical follow-up.

We arrived at the conclusion that uncomplicated diaphragmatic hernia gives no objective evidence of coronary artery disease. When chest pain is present, it is usually not associated with effort. With rare exceptions, when precordial or substernal pain on effort occurs in the presence of diaphragmatic hernia, the foregoing objective tests uncover the causative evidence of organic disease of the coronary artery.

A hiatus hernia may be the trigger mechanism in the precipitation of angina pectoris when coronary sclerosis exists. From both the physiological and clinical point of view, it is of interest that anemia, hematemesis or melena, severe diarrhea, vascular collapse or shock, all of which not infrequently occur in conjunction with diaphragmatic hernia, are precipitating factors in acute coronary insufficiency, especially in patients with antecedent coronary sclerosis. Co-existence of the two diseases is easily verified in this group, too, by the objective tests already enumerated.

"Hysterin"

A Hysterogenous Clot-Dissolving Substance

EMANUEL M. GREENBERG*

In 1945, the author reported the "non-clotting component of postpartum uterine blood."¹ This observation, together with the traditionally cryptic failure of menstrual blood to clot, led the author to determine whether the clotting failure was the result of the absence of one of the components necessary for clotting, or whether it was due to the presence of a clot inhibitor or a clot dissolver.

The presence of an anti-clotting uterine enzyme has been postulated for many years, and in 1946 the author, in a study of post-partum hemorrhage and the fourth stage of labor, first used the name "hysterin,"² for this as yet hypothetical thrombolytic substance.

A. Preparation of Hysterin: Human uteri, obtained at hysterectomy from the operating rooms of Beth Israel Hospital are being used. The tissue is ground and centrifuged, filtered and frozen. Some specimens were dry-frozen or lyophilized. Lyophilized extracts can, as powders, stand indefinitely and need only be redissolved with distilled water before use.

Purification including Berkefeld filtration and extraction studies will have to be carried out.

B. The Admixture of Freshly-drawn Venous Blood With "Hysterin."

20 cc. normal Saline + 10 cc. Venous Blood → Clot; latter was present at end of 72 hours.

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20 cc. redissolved lyophilized crude hysterin + 10 cc. Venous Blood → No Clotting after 72 hours—the blood cells form a sediment but can be easily resuspended by shaking.

C. The Admixture of Clotted Blood With "Hysterin."

20 cc. Crude Hysterin + Clot (first allowed to retract) → Dissolution of Clot in four hours.

Saline Control: Clot undissolved in four hours.

NOTE:—"In-vivo" studies are now being carried out and appear to be promising.

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* * *

*The Effect of d1-Methionine on the Healing of Surface Wounds**

S. ARTHUR LOCALIO, LEE GILLETTE, and
J. WILLIAM HINTON

Previous work (in press—Surgery, Gynecology and Obstetrics) indicates that d1-Methionine can bring the curve of healing of the hypoproteinemic rat toward normal. These experiments were performed on the abdominal wall of the rat. Since the healing of surface wounds is not primarily a process of fibroplasia, but one of contraction and epidermatization, this study is outlined to test the effect of d1-Methionine on the healing of surface wounds in the rat.

MATERIAL:

A total of more than 100 animals divided into 4 groups, were tested. The groups were as follows:

- 1) Normal animals
- 2) Normal animals that received d1-Methionine
- 3) Protein-depleted animals
- 4) Protein-depleted animals that received d1-Methionine

METHOD:

Areas of skin on the backs of the 4 groups of animals were excised, and the speed of healing was determined by the method of Douglas.

RESULTS:

The speed of healing of surface wounds of normal animals was determined. Secondly, the speed of healing of surface wounds of protein-depleted animals was determined.

It was found in the latter group that healing was markedly delayed.

Protein-depleted animals which received d1-Methionine manifested healing that was markedly accelerated as compared to the protein-depleted group which did not receive d1-Methionine.

The relationship of the accelerated healing and the enzyme activity of the sulphhydryl radical is discussed.

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The Surgical Treatment of Intractable Ascites by the Intramuscular Peritoneal Drainage Operation

JERE W. LORD, JR.

There are three important physiopathological states which lead to the formation of ascites. The first and most frequently observed one is cirrhosis of the liver. The second cause is the implantation of a malignant neoplasm on the peritoneum usually secondary to carcinoma of the gastrointestinal tract or the ovary but occasionally the neoplasm is primary such as a mesothelioma. Thirdly, cirrhosis of the liver due to repeated and long-standing congestive heart failure may lead to ascites.

The vast majority of patients with ascites obtain satisfactory relief by adequate management of the underlying condition. However, there is a significant group in which the ascites is intractable and will not respond to the best management requiring repeated paracenteses for relief. In patients with cirrhosis of the liver, whatever the etiology, not only is this a tedious and painful procedure but, of greater importance, the prolonged loss of protein often leads to cachexia and death. Similarly the control of ascites secondary to malignant peritoneal implants clouds the last weeks and months of many of these patients although in other respects they may be fairly comfortable.

An operative procedure has been devised

wherein the ascitic fluid is enabled to flow through the lumen of a glass button into a large subcutaneous pocket, the deeper aspect of which is formed by the muscles of the abdominal wall. Exposure of these muscles to the ascitic fluid is brought about by wide resection of the overlying deep fascia. Hence the fluid is absorbed continuously by means of the lymphatics in the muscles.

Eight patients with intractable ascites have been operated upon by the procedure outlined above. The cause of the ascites in six of them was portal hypertension associated with cirrhosis of the liver, while in two patients, the ascites was due to malignant peritoneal implants. The first patient in this series was operated upon in March 1947. The results have been as follows: complete subsidence of ascites in four patients; persistence of the ascites to a very mild degree without need for further paracenteses in two patients; failure in one patient, and one patient died two weeks post-operatively from massive hemorrhage. Experience with the patient designated as a failure, who was the second one in the series, led to improvements in technical details which have proven to be of value.

* * *

Prolongation of Action of Heparin

JEFFERSON J. VORZIMER, LEON SUSSMAN and MAXWELL MARDER

The anticoagulant effect of heparin was prolonged by incorporation of this substance in various menstrua. A concentration of 200-300 mg. per cc. of aqueous heparin solution emulsified in an equal quantity of menstruum composed of cholesterol derivatives (35%), peanut oil (65%), and beeswax (2%) gave the most satisfactory prolongation of the coagulation time. With this technique the coagulation time of the blood was

prolonged from 200 to 900% of normal for a period of 17 to 24 hours after a single intramuscular injection. The dosage of heparin varied with the weight of the patient, approximately 1½-2 mg. per pound body weight being required. There was no hemorrhage at the site of injection and pain was negligible. Further experiments involving the use of vasocostricators and other menstrua are being conducted.

*Aspiration of Bone Marrow from the Iliac Crest***Some technical and diagnostic advantages versus sternal aspiration*

MICHAEL A. RUBINSTEIN

The step-by-step technique of aspiration of bone marrow from the iliac crest is described, and its advantages versus the sternal technique are indicated.

The advantages of the iliac aspiration technique as presented here are: 1) *safety*, no serious injury can be sustained by any underlying organ; 2) *ease*, the procedure usually being less painful, and the patient being less apprehensive than when subjected to a puncture in the cardiac area; 3) *repeated aspirations*: iliac crest puncture can easily be performed at frequent intervals at both sides of the body, and is therefore very suitable for serial bone marrow studies. Moreover, the bone marrow cavities of the iliac crest can occasionally be used as a route of administering fluids into the general circulation when no intravenous route is available, and may perhaps allow for greater safety than the sternal technique.

Some disadvantage of iliac aspiration is occasional difficulty in puncturing the bone which at times may prove to be exceedingly hard.

The cells of the iliac bone marrow have been studied for the past four and a half years in about one thousand different cases showing normal and pathological findings. In about 300 of these instances, simultaneous sternal marrow studies were also performed.

The normal values of the iliac bone marrow, the total cellular count as well as the cell distribution, were found to have approximately the same range as those determined for the sternal aspiration. Normally the iliac crest contains hemopoietically active bone marrow in all age groups studied (age range 16-78 years).

Comparative studies of iliac and sternal bone marrow were performed in various instances of secondary anemia (posthemorrhagic, iron deficiency, nutritional type), hemolytic anemia (congenital and acquired

types, acute and chronic stages), aplastic anemia, pernicious anemia, sprue, osteosclerotic anemia and myelofibrosis, polycythemia, thrombocytopenic purpura, agranulocytosis (following thiouracil and sulfonamides), Banti's syndrome, Gaucher's disease, Tay-Sach's disease, Hodgkin's disease, follicular lymphoblastoma, leukemias, lymphosarcoma, multiple myeloma; various infectious diseases, kidney diseases, cirrhosis of liver, and various neoplastic diseases with or without evidence of bony metastases.

In most of the cases studied the findings from both sources run parallel, and the iliac marrow presents the characteristic picture of the disease as seen in the sternal aspiration.

However, in certain instances the iliac aspiration has proved of distinct diagnostic advantage, as compared to the sternal aspiration alone. The instances where iliac aspiration has provided more diagnostic information than the sternal technique included some cases of infiltrative diseases of the bone marrow, such as 1) early stages of multiple myeloma; 2) metastatic lesions of various neoplastic diseases; 3) early cases of lymphatic leukemia; 4) miscellaneous diseases with patchy distribution in the bone marrow, such as a case of Gaucher's disease and some cases of osteosclerotic anemia. It is apparent that in some of these instances the disease process may invade one part of the bony system earlier than another. This would explain the fact that in some cases the iliac aspiration proved diagnostic of the disease, while the sternal aspiration was non-diagnostic; in some other cases the reverse was true. Combined sternal and iliac bone marrow studies are indicated wherever patchy character of the disease process is suspected.

Examples are abstracted where the diagnosis was arrived at on the basis of iliac bone marrow studies.

* From the Medical Division, The Montefiore Hospital, New York, N. Y.

Also two instances are abstracted to show the advantages of iliae puncture technique enabling serial studies. In one case clumps of melanine-laden cells were found in the iliae crest aspiration while the sternal marrow was negative for these cells. Following thiouracil administration the melanuria stopped and studies of iliae bone marrow at six hours interval showed gradual disappearance of melanine in the cells. In another case of pernicious anemia in relapse and

treated with folie acid, the successive stages of maturation of megaloblasts were studied in serial iliae aspirations performed at four hours intervals.

SUMMARY

Bone marrow can be obtained safely, easily and repeatedly from the iliae crest, and may provide information at times not obtainable from the sternal aspiration.

* * *

The Diagnosis of Thyroid Disease by Means of Radioactive Iodine

STEPHEN BENNETT YOHALEM

The administration of radioactive iodine is followed by concentration of the substance in the thyroid gland. The ordinary Geiger-Müller tube has a large angle of acceptance. By means of a lead enclosure a collimating device has been made with which the radioactivity in adjacent areas may be measured separately. These measurements

plotted against distance across the neck from the midline or against distance from the vertex produce curves designated as profiles which permit increased accuracy in the diagnosis of thyroid disease when considered with the physical findings. Sixty patients have been so studied and the results in a variety of affections are demonstrated.

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BULLETIN OF
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JULY 1948

BCG AND THE NEWER EPIDEMIOLOGY
OF TUBERCULOSIS*

KONRAD BIRKHAUG

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HERE are two ways of preventing tuberculosis, the segregation of infection and the immunization of persons who may be exposed to infection. Both courses are followed in European countries but in the United States we have neglected the second. It is said that the elimination of infection is the direct and logical way of controlling tuberculosis and surely it has succeeded well in our own country. Yet, to continue to be logical, one must admit that it is a method which will pay diminishing returns the better it succeeds and there are reasons to suspect that the further segregation is carried, the more important vaccination may become.

Immunization against tuberculosis is the kind of prevention C. E. A. Winslow may have had in mind when he wrote: "Prevention is a cure really effected in time." This is what may be expected of BCG (*Bacille Calmette-Guérin*) and what has been achieved with it in many controlled studies abroad. To be candid one must admit that foreign experts

* Given January 8, 1948 at the Stated Meeting of The New York Academy of Medicine.

find the American attitude puzzling and shortsighted. The foreign workers admit the unfortunate discrepancies which marred the initial studies in man, but they consider that later work has overcome those defects and firmly established the value of BCG vaccination. And they seem to have been more alert to the changing tuberculosis picture and the growing importance of vaccination as the frequency of infection is reduced or delayed.

I would like to discuss the place of vaccination in tuberculosis from this point of view.

It is perfectly true that tuberculosis control programs in the United States have yielded unprecedented results which promise to eradicate the disease completely in the very immediate future and that the death rate from tuberculosis has fallen steadily from 200 to 36 per 100,000 population during the last forty years.¹ This meritorious record is exceeded only by that of little Denmark, where during the same period tuberculosis mortality has been reduced from almost 300 to 32 per 100,000 population. And Denmark was one of the first countries to avail herself of BCG vaccination. Today this vaccine is being used extensively throughout Denmark on her tuberculin negative population under 50 years of age.²

At length the sentiment toward BCG has changed in the United States and governmental medical authorities have come to believe that the requirements of safety for the use of BCG in man have been fulfilled and that its effectiveness has been proved on more than an experimental scale. Thus we have seen recently two official attempts being made by the United States Public Health Service³ and by the New York State Department of Health, in coöperation with The Medical Society of the State of New York⁴ to use BCG in groups of individuals exposed to special risks of infection, such as student nurses, medical students, hospital personnel, inmates in mental hospitals, and generally among the Indian and Negro populations.

In spite of the present relatively low level of tuberculosis in the United States, last year more than 50,000 deaths from tuberculosis occurred in this country, of which 6,600 died in the State of New York alone. The majority of these victims are between 20 and 45 years of age—that relatively brief life span on which the nation depends so much for its strength. And each of these deaths represents nine cases of frank tuberculosis. This places the number of tuberculosis patients at 500,000.

Only half of these individuals are known to be under treatment, and only one-fourth in hospitals and sanatoria. Epidemiologically speaking: approximately 180,000 frank cases of tuberculosis are left at large to infect the healthy population in the United States.⁵

Most countries present a similar epidemiological tuberculosis situation although in varying degrees of severity. It exists in the Scandinavian countries where the cost of maintaining tuberculosis patients and their families becomes an excessive drain on governmental and private funds. For this very reason these small countries are pushing the tuberculosis control programs to the limit with compulsory tuberculin test surveys, miniature chest x-ray examinations and isolation and treatment of all known cases of the disease. In addition to the time-honored tuberculosis control measures, Denmark, Norway and Sweden have concordantly entered upon nation-wide BCG vaccinations of the susceptible tuberculin negative population under 50 years of age in a frantic effort to reduce tuberculosis mortality and morbidity to a minimum within the shortest possible time. While BCG vaccination remains on a voluntary basis in Denmark and Sweden and proceeds successfully, the intransigent antivaccination sentiment, which is dominant over all of Norway, compelled the Norwegian parliament of December 8, 1947, to make BCG vaccination compulsory for all tuberculin negative persons under 50 years of age.

Having for the past 16 years been intimately associated with experimental and clinical BCG studies, beginning at the University of Rochester School of Medicine in 1930,⁵ continuing with the late Professor Calmette at the Pasteur Institute in Paris in 1932,⁶ and as director of the National BCG Laboratory at Bergen, Norway until the fall of 1945⁷ and at the present time in charge of the BCG Laboratory of the New York State Department of Health, Division of Laboratories and Research,⁸ I have come to know the limitations and possibilities of tuberculosis control with the BCG vaccine. I consider it a great honor, therefore, to be asked to address you on this contested subject.

ARTIFICIAL IMMUNIZATION AGAINST TUBERCULOSIS

The fact that most persons who become infected with tubercle bacilli survive the infection without manifesting other signs than a positive tuberculin reaction proves that man is endowed with a high capacity for acquiring resistance against tubercle bacilli. This fact

incited early investigators to do for tuberculosis what Jenner did for smallpox and Pasteur for anthrax, namely to produce a vaccine which might ward off tuberculous disease.⁹ It soon became apparent, however, that such a vaccine must stimulate the production of a primary tuberculous complex as well as a positive tuberculin reaction in order to enhance the native resistance in animals and man to virulent tubercle bacilli.¹⁰

The attempts to imitate the real disease without producing progressive tuberculosis are legion and include injections with only a few virulent bacilli, which proved to be a highly dangerous procedure¹¹ or with killed tubercle bacilli which produced a wholly inadequate resistance against a virulent infection.¹² The only successful attempt is BCG vaccine. This consists of living bovine tubercle bacilli which lost their original virulence by being cultured on glycerine-bile potato medium during more than 200 bi-weekly passages. The laboratory manipulation was started in 1906 by the late Albert Calmette, and his veterinary assistant, Camille Guérin.¹³ After 15 years of solidly founded immunization studies in laboratory animals and in cattle, Calmette¹⁴ declared that BCG had become completely attenuated in its virulence. He also proved that BCG induced in the animal tuberculous tissue which was indistinguishable from that of the real disease and that the vaccinated animals became tuberculin positive as well as highly resistant against virulent tubercle bacilli. Calmette was careful, however, to call attention to the fact that this immunity was of a special type which should not be confused with the more absolute immunity induced, for example, by an attack of typhoid fever or smallpox. Nevertheless, Calmette maintained that BCG produced enough resistance to overcome a light infection with virulent tubercle bacilli and that if the latter could be superimposed on BCG vaccination, preferably during the first few months after vaccination, then the relative BCG immunity would be converted into an absolute immunity.¹⁵

It is most regrettable that the magnificent experimental BCG studies of Calmette and his associates, which were carried on in controlled series on animals and cattle, were not continued on the same high level following 1921 when Calmette permitted BCG vaccination of newborn infants.¹⁶ Calmette argued, however, that his clear-cut results with animal immunization warranted an uncontrolled mass vaccination program in France on all newborn infants. In order to make this anti-

tuberculosis scheme a success, Calmette advocated the oral administration of BCG.¹⁷ When this method failed to produce a tuberculin positive reaction in the majority of vaccinated infants, Calmette argued that allergy was not an essential attribute to immunity.¹⁸ By the end of 1928, in France alone, 116,180 infants had been vaccinated with BCG¹⁹ and by 1930, the number had risen to 210,000.²⁰

When Calmette presented statistics to prove that the BCG vaccine actually produced a high degree of protection against tuberculosis in infants intimately exposed to infection, shrewd statisticians in England²¹ and on the European continent²² discovered with dismay that the evidence was based on a comparison of the tuberculosis death rate among vaccinated infants between the ages of one month—to allow for the development of immunity in those vaccinated at birth—and four years, and among nonvaccinated infants in the general population. In some analyses, the simpler figure of deaths from all causes among vaccinated infants as compared with that for the entire population was employed.

The most serious criticism, however, arose from the discovery that many of the vaccinated infants had not been followed up and that autopsies had not been performed on individuals whose deaths were ascribed to nontuberculous diseases.²³ Then followed the unfortunate Lübeck tragedy in 1930 which unjustifiably was ascribed to BCG. In reality it was caused by the substitution in Lübeck of a strain of virulent human tubercle bacillus for BCG.²⁴

It is needless to discuss any further Calmette's sins of omission. They have been critically and scholarly reviewed in K. Neville Irvine's book, *The B.C.G. Vaccine*,²⁵ and by G. Gregory Kayne's²⁶ scrutinizing analysis of the scientific and practical aspects of BCG vaccination up to 1936.

The present position of BCG is succinctly and critically set forth by Professor W. H. Tytler²⁷ in a "Memorandum on B.C.G." which was prepared in the fall of 1946 for a Joint Committee of the British Tuberculosis Association, the Joint British Tuberculosis Council and the British National Association for the Prevention of Tuberculosis, for the consideration of the Minister of Health and the Secretary of State for Scotland. Briefly, these deputations "believe:—

- (a) That the harmlessness of B.C.G. is established beyond doubt by practical use on a scale exceeded only by a few proved methods of immunization, such as those for smallpox, diphtheria, and the enteric infections.

- (b) That a very considerable degree of immunizing efficiency is indicated by the most reliable results from other countries, particularly those from Norway and Sweden.
- (c) That there exists in the Tuberculosis Services of Great Britain, and among the medical profession generally, an active and widespread desire that a reliable supply of B.C.G. vaccine should be available here, as it has been for years in most other countries of the world.
- (d) That the application by "multiple puncture" or by "scarification," judged by results so far published, promises to remove one of the most serious obstacles to the general use of B.C.G., the occurrence of abscesses at the site of injection."

I have since been informed by English colleagues that their government has acted favorably on this request and that a national BCG Laboratory is already under construction near London.

On September 7, 1946, a conference on BCG vaccination was held in the offices of the Tuberculosis Control Division of the United States Public Health Service in Washington, D. C., which was attended by outstanding leaders in tuberculosis in the United States, China and Denmark. This conference recommended that investigations be continued during 1947 on certain population groups in the United States (Columbus, Georgia) in order to determine the effectiveness of BCG in the control of tuberculosis. This work is already in progress.²⁸

The greatly extended tuberculosis control program in New York State includes the establishment of a laboratory for the preparation and study of the BCG vaccine and of a BCG Advisory Committee composed of members from the Division of Tuberculosis Control and the Division of Laboratories and Research, in coöperation with The Medical Society of the State of New York. Following several discussions of the scientific and practical aspects of BCG vaccination, the BCG Advisory Committee unanimously approved of the official BCG Vaccination Program for the State of New York.²⁹ The opening paragraph of this significant document reads:

"At the present time, BCG vaccination is the only known practical method of reducing morbidity and mortality from tuberculosis. There is general agreement on two points: (a) it is safe; (b) it serves to convert nonreactors to tuberculin to reactors through infection with avirulent and *benign bovine* tubercle bacilli. There is sufficient evidence of the effectiveness of BCG to warrant its use in selected population groups in which the infection rate is high. Persons in such groups might otherwise be infected with virulent organisms. BCG vaccine is not to be administered indiscriminately, because it can be of benefit only to those persons who have NOT been infected by the tubercle bacillus. It must be emphasized that BCG vaccine has NO value in the treatment of tuberculous disease."

The BCG Vaccination Program is already in progress throughout

New York State. During 1947 more than 1,500 tuberculin negative nurses, medical students, hospital and sanatoria employees have been vaccinated with BCG by the multiple puncture method.³⁰ This program will gradually be extended to mental hospitals and population groups with high tuberculosis morbidity and mortality rates, such as the Negroes and the Indians.

The main contributory factors to this official recognition of BCG vaccination in the United States Public Health Service and in the New York State Department of Health and The Medical Society of the State of New York must be sought in the considerable BCG vaccination material which has accumulated in the Scandinavian countries and which because of World War II has but recently become available in the English medical literature. This material implies that BCG vaccination is a logical step in view of the new epidemiological situation which has arisen by postponement of primary tuberculous infection from childhood to early adult age when such infection tends to produce a severer type of caseo-pneumonic tuberculosis which rapidly progresses within a few months to advanced pulmonary tuberculosis, without any evidence that the latter is due to a new exogenous reinfection. In the following I shall draw heavily upon these newer aspects of the epidemiology of tuberculosis.

TUBERCULIN SURVEYS AND PRIMARY TUBERCULOUS INFECTION

The first response to infection with virulent tubercle bacilli depends on the native resistance of the host and the virulence and number of invading microorganisms. In the presence of a high native resistance, the only manifestation of primary infection with tubercle bacilli may be a positive tuberculin reaction. If the reverse is true, the pathological response may vary from a mild influenza-like attack of fever, cough and expectoration to a rapidly progressive and generalized disease which may terminate fatally. Fortunately most infected persons experience a silent primary tuberculous infection which is diagnosed if at all by a positive tuberculin reaction. The importance of the tuberculin test in epidemiological surveys is now universally recognized as a potent weapon in the control of tuberculosis. Its employment in mass examinations has already yielded some new and useful information.

The rapid decline in tuberculosis mortality that we have observed during the last forty years in the United States is also reflected in a

rapid decline in the incidence of infection with tubercle bacilli and in the age-distribution of such infection. The old view that most persons passing out of childhood have already been infected as indicated by a positive tuberculin reaction, is no longer tenable. Today it is not unusual to discover by tuberculin surveys that almost the entire rural and large portions of the urban populations under 15 years of age are tuberculin negative reactors. The most significant declines are usually observed in communities where intensive tuberculosis control measures have been carried out.³¹

The question which has naturally arisen is the fate which awaits tuberculin negative young adults who have forfeited the chance to acquire specific resistance against tubercle bacilli by means of a mild childhood infection, when such persons become exposed to massive tuberculous infection later in life. Experience with native races has clearly shown that such tuberculin negative adults are by no means bound to develop serious tuberculosis as a result of a sudden exposure to infection. When in good physical condition, the majority may escape manifest tuberculosis. But under unusual stress, such intimate and prolonged exposure may lead to serious disease which may terminate fatally.

This point became subject to a ten-year tuberculin survey of school-children passing out of the eighth grade and until they reached adult life. Ingebrigtsen³² tuberculin tested all the eighth graders in the Norwegian fishing town Stavanger, with a population of 46,000. The average age was 14 $\frac{3}{4}$ years and 20 per cent reacted positively with 0.5 mg. tuberculin injected intracutaneously. Tuberculosis mortality records for Stavanger proved that only 2 per cent of all deaths from the disease occurred during the school age from 7 to 15 years. Ten years later, the same group of now 25-year-old individuals, were retested with the same dose of tuberculin and 73 per cent were tuberculin positive reactors. Twenty per cent of all deaths from tuberculosis in their town occurred during the decade between 15 and 25 years of age. Ingebrigtsen concludes from this study that "most young people leave school nowadays without that significant specific resistance against tubercle bacilli which tuberculin positive reactors possess. The tragic fate that awaits them during the first decade after they leave school makes it imperative that BCG vaccination should be made available to all tuberculin negative reactors in order to enable them to ward off successfully an attack of virulent tubercle bacilli."

LACK OF CHILDHOOD BOVINE INFECTION COMPENSATED BY BCG

Denmark's "grand old man" in medicine, Professor Thorvald Madsen³³ has recently contributed an important chapter to the epidemiology of tuberculosis. He has compared the fate of young people on the island of Bornholm, where bovine tuberculosis has been eradicated for more than twenty years and human tuberculosis among the 46,000 inhabitants is nearly eliminated, with a similar group in the town of Haderslev on the mainland where 75 per cent of the population is infected with bovine tubercle bacilli. He finds that no great difference in tuberculosis mortality or new cases existed in the two districts. But in Bornholm only 7 per cent were tuberculin positive reactors at the age of 7 and 15 per cent at the age of 14 years. In Haderslev, on the other hand, the figures were 45 and 75 per cent, respectively. But in spite of the heavy infection rate in Haderslev, deaths from tuberculosis were not more numerous there than in Bornholm. It was apparent, therefore, that by pooling the milk from many dairies in Haderslev before the milk was delivered for consumption, a general mild infection with bovine tubercle bacilli took place which failed to develop into manifest and clinical tuberculosis. Yet it was sufficient to produce tuberculin allergy in 75 per cent of the population at the age of 14 years and a considerable immunity against subsequent severe attacks of tuberculosis, for it was shown that persons who drank milk from a single and highly infected cow, became severely ill and often died from tuberculosis. Because there is not enough active tuberculosis in Bornholm, where every person is tuberculin tested and chest x-rayed and all known cases of the disease are isolated in hospitals, the incidence of tuberculin negative reactors is increasing and there are ten times more cases of tuberculous disease needing hospital treatment than in bovine tuberculosis infested Haderslev. One may ponder whether eradication of bovine tuberculosis is in the best interest of man!

A most important observation has been made in Bornholm, however: that the primary tuberculous complex produced in tuberculin negative reactors by means of BCG vaccination, is sufficient to protect against the progression of a subsequently superimposed virulent infection. For "it was discovered," Madsen writes, "that the first cases of tuberculous disease occur only rarely amongst individuals with positive reaction to tuberculin, and only when these persons are submitted to a very strong

infection. The victims are nearly always those with a negative (tuberculin) reaction."

"Under these circumstances," Madsen continues, "the young persons having a negative (tuberculin) reaction have become more and more numerous; in a great number of country schools all the children react negatively. This state of affairs is perfect as long as these persons remain on their island, where the possibilities of infection are becoming constantly less. If they leave the island, however, to go to Copenhagen or elsewhere . . . where they are exposed to tuberculous contagion, these persons with negative (tuberculin) reaction often contract serious, even fatal tuberculosis. This has been observed amongst young men called up for military service and young girls taking up work as domestic servants, etc. For this reason, Calmette's (BCG) vaccination has begun to be carried out on a large scale. It is not only carried out on persons having a negative (tuberculin) reaction before they leave the island but has gradually been generalized in all the schools for children and adolescents, in the day-nurseries, barracks, police force, etc. and the results have been excellent," Madsen concludes.

LATE PRIMARY TUBERCULOSIS AND BCG VACCINATION

The distinguished Danish tuberculosis expert, Johannes Holm,³⁴ has recently presented a critical analysis of BCG vaccination in Denmark, which should be scrutinized for first-hand information on a nation-wide BCG program. He mentions an epidemic of primary tuberculosis in a school for girls between 12 and 19 years of age. A group of 133 tuberculin negative pupils had been vaccinated with BCG and had become tuberculin positive reactors, but 105 tuberculin negative pupils in the school had not been vaccinated. An influenza-like epidemic among the pupils in the classes of a woman teacher who suffered with pulmonary tuberculosis occurred in this group. Among the 105 nonvaccinated tuberculin negative pupils, 40 per cent presented chest x-ray changes; 35 per cent had tubercle bacilli in their sputum or gastric washings, and 6.5 per cent developed pulmonary tuberculosis. Among the 133 BCG vaccinated pupils, no chest x-ray changes were observed, *i.e. no primary tuberculosis*, and only 1.5 per cent developed pulmonary tuberculosis, in contrast with 3.1 per cent pulmonary tuberculosis among 130 originally tuberculin positive pupils on entry. "All told," Holm concludes, "it seems safe to state that BCG vaccination gives an

almost complete protection against the morbid conditions accompanying the tuberculous primary infection and also a considerable degree of protection against genuine pulmonary tuberculosis. This protection, however, is not absolute, since in every fairly large group, there will be a few instances of pulmonary tuberculosis among the BCG vaccinated subjects."

One cannot discuss tuberculosis control of late primary tuberculosis with BCG vaccination without pausing in reverence before the classical observations made on the subject by Johannes Heimbeck,³⁵ called "The Father of BCG Vaccination in Norway." Before he actually embarked on BCG vaccination of nurses at the Ullevaal Communal Hospital in Oslo some twenty years ago, Heimbeck made the startling observation that the victims of tuberculosis among student nurses working on tuberculosis wards are nearly always the tuberculin negative reactors. Thus he found that among 280 negative reactors on entry, 22.4 per cent developed tuberculosis and 3.6 per cent died from the disease in contrast to only 0.9 per cent disease and no deaths during the same observation period of 625 who were tuberculin positive reactors on entry.

The second phase of Heimbeck's studies was inspired by a desire to mitigate the high incidence of tuberculous disease among tuberculin negative student nurses. Thus he was the first physician in Norway to suggest the use of BCG vaccination in tuberculin negative reactors who were compelled in line of duty to work in a tuberculous environment. The immunization work was carried out on a voluntary basis and thus a control series became available of those who refused vaccination with BCG. From the very start, he made use of the injection method against the advice of Calmette that the oral method was adequate. This was imperative for Heimbeck's purpose to render the tuberculin negative student nurses positive reactors as soon as possible by means of BCG. The oral administration of BCG fails to do so in the majority of cases.³⁶ When the vaccinated student nurses had been converted to positive reactors they were admitted to the hospital wards together with the nonvaccinated tuberculin negative reactors and the naturally positive reactors. After the customary 3 years' training, Heimbeck observed among 287 successfully vaccinated student nurses 2.6 per cent tuberculosis and 0.2 per cent deaths from the disease in contrast with 17.6 per cent tuberculosis and 1.8 per cent deaths among 107 nonvaccinated and tuberculin negative nurses on entry.

Heimbeck³⁷ now has records of 1,453 student nurses. The tuberculosis morbidity rate per 1000 observation years is 12.4 for originally positive reactors, 24.1 for BCG vaccinated nurses and 141.2 for non-vaccinated negative reactors on entry. Heimbeck subscribes to Holm's³⁴ conclusion that BCG vaccination protects almost completely against primary tuberculosis and that the incidence of clinical pulmonary tuberculosis is significantly reduced.

The late Olaf Scheel³⁸ obtained similar results in medical students at the University at Oslo, but with rather less marked differences. Malmros and Hedvall³⁹ experienced the same striking differences among the vaccinated and nonvaccinated medical students at the University at Lund in Sweden.

Ferguson's⁴⁰ more recent study in Canada also confirms Heimbeck's statistical evidence on the protection of nurses with BCG. He extended vaccination to other hospital employees. In eight Saskatchewan hospitals and three tuberculosis sanatoria, 1,005 nurses and 470 employees negative to tuberculin were vaccinated intracutaneously with BCG. The results were compared with 759 tuberculin negative and nonvaccinated nurses and 274 employees. After an exposure of both groups to open tuberculosis for an average of two and one-half years, Ferguson found that vaccination with BCG reduced tuberculosis by from 76 to 80 per cent or to approximately the same low level as among the originally tuberculin positive reactors. He also noted that the tuberculous disease which developed among the BCG vaccinated nurses and hospital employees was of a more benign type than that seen in the nonvaccinated persons of whom four-fifths required hospital treatment while only two-thirds of the vaccinated persons required such care. One death from tuberculosis occurred in the nonvaccinated group and none in the vaccinated group. These results must have impressed Ferguson greatly for he states that "the serious situation that had been developing with regard to excessive incidence of tuberculosis among nurses and sanatoria employees who did not react to tuberculin on entering the environment, during the period 1930 to 1938, has not been present since vaccination of negative reactors was begun in September, 1938. The nursing schools and the League in Saskatchewan no longer have anxiety and worry with regard to excessive tuberculosis developing among their negatively reacting staff."

Four outstanding contributions to vaccination with BCG in the

United States have confirmed the impression abroad that BCG is an important measure for the prevention of tuberculosis in newborn infants and in early adult life. Rosenthal, Blahd and Leslie⁴¹ have carried out a ten years' BCG vaccination program in newborn infants at the Cook County Hospital in Chicago. Their study comprises 2,831 infants, of which 1,414 were vaccinated by the multiple puncture method four to six days after birth. A similar group of 1,417 infants served as non-vaccinated controls. The observation period varied from 3 months to 9 years. Both groups are comparable for age and race distribution. Although all the children came from homes free from tuberculosis, as proved by chest x-ray films of all family members, all subjects lived in areas in Chicago that have high tuberculosis mortality rates (100 to 300 per 100,000 population). The children were followed up more or less regularly at semi-annual intervals with physical examination, tuberculin tests and chest x-ray films. Among 1,204 vaccinated children with no history of definite tuberculous exposure, 3 cases of tuberculosis with 1 death occurred in contrast to 23 cases of tuberculosis with 4 deaths among 1,213 nonvaccinated controls of the same category. However, among 98 vaccinated children with a definite history of exposure, 1 case of tuberculosis and no deaths occurred whereas among 63 similarly exposed nonvaccinated controls, 4 cases of tuberculosis with 3 deaths occurred. Rosenthal concluded from this extensive study that "during the first seven years of life, BCG vaccination is of definite value in the prevention of tuberculosis."

Some 13,000 chest x-ray films accumulated during Rosenthal's investigation. Recently these roentgenograms have been examined by Neiman and Loewinsohn⁴² for hilum densities, enlargements and outlines. Any evidence of abnormalities was followed up with frequent serial films in order to determine the nature of the lesions. Parenchymal densities were likewise re-examined. Only parenchymal densities which persisted for a period of months were included in the final analysis, and calcification was diagnosed only by characteristic formation, outline and refractility. From this laborious analysis to assess the value of BCG as a preventive for primary tuberculosis, these authors concluded that "children vaccinated with BCG tend to show less primary tuberculosis as determined by roentgenographic examination than nonvaccinated children," the rate being 2.46 in the former and 6.92 in the latter, a difference which has absolute statistical significance ($X^2 = 14.2825; P = 0.0002$).

The demonstration that BCG actually inhibits primary tuberculosis in infants and children confirms a similar study by Kereszturi, Park and Logie⁴³ in 1935 of 2,900 chest roentgenograms taken of 417 BCG vaccinated and 564 nonvaccinated control infants in tuberculous families in New York City. These roentgenograms revealed that 4 per cent of the vaccinated children that had become tuberculin positive later developed pulmonary lesions detectable by x-ray, but none developed lesions of the primary complex type, and only one developed calcification of a peribronchial lymph node. Among the nonvaccinated controls, however, 17 developed an unmistakable roentgenological primary complex of which 13 were calcified, and 9 others developed calcified lesions of the bronchial lymph nodes. These carefully controlled and followed up long term studies confirm and re-affirm what has been stated repeatedly in this address, namely that vaccination with BCG inhibits primary tuberculosis in a manner analogous with the specific resistance induced by a spontaneous and clinically silent infection with virulent tubercle bacilli. Apparently it does more, since the incidence of clinical pulmonary tuberculosis is also significantly reduced by means of BCG vaccination.

This becomes quite evident in Aronson and Palmer's⁴⁴ six years' experience with BCG vaccination among North American Indians. This important analysis from a heavily infected milieu comprises 3,007 Indian persons ranging in age from one to twenty years inclusive. Of these, 1,550 were injected with 0.1 or 0.15 mg. BCG while an identical group of 1,457 were injected with 0.1 ml. of sterile physiological saline solution in an apparent attempt to confuse any psychological influence which might prove prejudicial in favor of vaccination. No change was attempted throughout the study in the living conditions of the persons under investigation, including exposure to tuberculosis. With relatively few exceptions, an initial chest x-ray film was taken and this was repeated annually for six years together with tuberculin tests. Revaccinations are not mentioned and some lots of vaccine seemed less suitable than others and may have influenced the immunity response. Tests of the vaccinated and control groups as to age, amount of exposure to tuberculosis, and completeness of the follow-up examinations indicate that the two groups are as comparable as humanly possible in these respects.

During the six-year period of this study, 68 deaths from all causes

occurred in the nonvaccinated controls as compared to 34 in the vaccinated group. Twenty-eight deaths from tuberculosis were definitely proved in the controls and only 4 such deaths among the vaccinated. Including those that died from tuberculosis, 48 cases were classified as having extrapulmonary tuberculosis or advanced pulmonary lesions in the control group and only 9 in the vaccinated group. There were 20 cases in the control group showing minimal chest x-ray lesions and only 8 among the vaccinated. The corresponding figures for cases showing enlarged hilar glands were 99 and 19, respectively, and for pleural effusion 18 and 4, respectively. When the total incidence of cases of all types and deaths were tabulated, there were 185 among the nonvaccinated controls and only 40 among the vaccinated persons. In terms of cases per 1,000 person-years, the rates were 24.3 and 4.7, respectively.

Encouraged by the marked protection induced by BCG vaccination against the development of primary tuberculosis as well as clinical pulmonary tuberculosis as measured both by mortality and morbidity rates in the nonvaccinated and vaccinated groups, the United States Bureau of Indian Affairs plans to use BCG vaccine as a routine procedure in the Indian Service, at least in the areas of high infection. Aronson⁴⁵ stated in a recent popular article that "under the program, all babies born in the Service's hospitals will be vaccinated within a few days, and later, children will be tuberculin tested in school. It is hoped that this procedure, along with health education and sanatorium treatment, will cause the disease to be reduced rapidly." Aronson holds that "the choice of Indian reservations for the determination of the effectiveness of the BCG vaccine was a fortunate one, for the Indians represent a relatively homogenous racial group; their habitation, whether tent, tepee, hogan, wickiup or house is overcrowded, sleeping facilities are inadequate and the density of population per bed or pallet is high. Food, clothing and heating facilities are inadequate and irregular."

RE-ORIENTATION TOWARD BCG VACCINATION

It is only in recent years that BCG vaccination has assumed increased importance for the adult population which has escaped a primary infection with tubercle bacilli in childhood. Extensive clinical, roentgenological and histopathological investigations have been carried out especially in Sweden and Norway by Malmros and Hedvall,⁴⁶ Frostad,⁴⁷ and Hedvall,⁴⁸ which show that primary tuberculosis is becoming usual in adults

and that clinical pulmonary tuberculosis arises to a great extent as a consequence of this. Frostad's conclusion that "the destructive form of the pulmonary tuberculosis appears in most cases in close relation to the primary infection, generally less than 12 months afterwards," is partly shared by Hedvall⁴⁸ and Malmros.⁴⁹ The former writes that "in places where the disease is still to a great extent severe the tuberculosis *can*, shortly after the primary infection (even after one or two months) begin to develop from the primary focus itself or its immediate surroundings. The lung lesions are then of the nature of an infiltrate and show no definite apical localization. The continued development is often characterized by a tuberculous pneumonia undergoing liquefaction." And Hedvall continues that "in places where the course of the tuberculosis is milder, the first lesions are as a rule characterized by initial foci with a definite preference for the uppermost part of the lung. The investigations of Frostad and Malmros-Hedvall, which include material from places with tuberculosis of varying severity, are not therefore conflicting. On the contrary, they supplement each other in a fortunate way. Frostad's cases represent the acute development, those of Malmros-Hedvall the subchronic or chronic development after a primary infection." But the general impression prevails in Scandinavia that progressive pulmonary tuberculosis develops in close conjunction with primary infection. This view has influenced the policy toward BCG vaccination in Denmark, Norway and Sweden since all of the controlled investigations to date have proved that the first victims of tuberculosis are invariably tuberculin negative reactors. The seriousness with which this view is embraced is best illustrated by the fact that nowadays no tuberculin negative student nurse or medical student is admitted to nursing schools and medical faculties in Scandinavia unless they are willing to become vaccinated with BCG. Vaccination became extremely popular in Scandinavia during the World War II and has since become extended in Denmark and Sweden to all tuberculin-negative reactors over 14 years of age on a voluntary basis and since December 8, 1947, BCG vaccination has become obligatory in Norway for all negative reactors under 50 years of age.

With the notable exception of the United States Public Health Service and the New York State Department of Health, it is indeed regrettable that the efficacy of BCG vaccination is still a matter of dispute among authoritative tuberculosis experts in the United States and that

the National Tuberculosis Association still is aloof to any official recognition of the value of the vaccine. This intransigent attitude is perhaps in the process of being changed now that the World Health Organization in the United Nations is recommending extensive use of the BCG vaccine and is already dispatching numerous BCG teams to the war-stricken European countries.⁵⁰ The erudite editor of *The American Review of Tuberculosis*, Max Pinner, wrote in the October issue of the official journal of the American Trudeau Society⁵¹ as follows:

"As is so clearly stated in Doctor Malmros' (4) paper, BCG vaccination is the logical consequence of the epidemiological situation in Scandinavia. If it should prove to be true for the United States that a large proportion of progressive tuberculosis in adults develops independently of a second exogenous infection, our present strategy of antituberculosis work would need fundamental reforms."

CONCLUSIONS

Experimental studies and clinical experience prove that a spontaneous primary infection with tubercle bacilli which renders the organism hypersensitive to tuberculin confers an incomplete but relatively significant resistance against a subsequent tuberculous infection, and that the first victims of tuberculous disease are tuberculin-negative individuals who have escaped a spontaneous and non-progressive primary tuberculous infection.

A direct result of the modern trend to defer the primary tuberculous infection from childhood to adult life is an increasing susceptibility among tuberculin-negative individuals of early adult age to contract a serious clinical tuberculosis when they are intimately exposed to infection with tubercle bacilli.

This modern trend in the epidemiology of tuberculosis has brought about a reorientation toward the use of artificial immunization against tuberculosis by means of killed or attenuated living tubercle bacilli. So far, only the avirulent and living BCG (*Bacille Calmette-Guérin*) vaccine has produced regularly hypersensitivity to tuberculin and a significant protection against tuberculosis in millions of people over more than twenty years.

There exists a lamentable lack of unassailable statistical proof of the effectiveness of BCG under rigidly controlled conditions in man, although such evidence is highly suggestive in animal experimentation. Nevertheless, universal unanimity obtains as to its harmlessness and near unanimity in regard to its almost complete protection against the

clinical manifestations of post-primary tuberculosis in children and an incomplète but highly significant protection against clinical pulmonary tuberculosis in adults.

BCG vaccine should be recommended for extensive use in the United States in tuberculin negative reactors in groups occupationally exposed to tuberculous infection and in population groups with high tuberculosis mortality and morbidity, and where there has been a known exposure to tuberculosis or where an exposure is likely to occur.

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PRIMARY ATYPICAL PNEUMONIA AND INFLUENZA* DIAGNOSIS, PREVENTION, TREATMENT

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INTRODUCTION

To discuss adequately the diagnosis, prevention and treatment of both primary atypical pneumonia and influenza in a period of one hour is not an easy task. The undertaking is difficult chiefly because of the defects in present knowledge concerning these two different conditions. It is true in general that the less certain is knowledge of a disease the more time is needed to discuss critically such information as exists concerning it.

With respect to the establishment of a diagnosis in either of these two illnesses present evidence indicates that specific laboratory procedures are available which permit of a definite diagnosis of influenza; no similar procedures have been developed as yet for primary atypical pneumonia and consequently a considerable body of clinical, x-ray and laboratory evidence is needed before a relatively secure diagnosis can be made. Concerning the prevention of either of these two maladies the available evidence indicates that means have been devised which make it possible to induce relative immunity against influenza for a period of a few months; no similar procedure is available as yet for primary atypical pneumonia. Regarding the treatment of either of these two ailments existing evidence indicates that the symptoms of both can, to a considerable degree, be relieved by the use of various well known and well tried procedures; there is as yet no specific therapeutic agent which will significantly alter the course of either condition.

DEFINITION OF TERMS

At the outset it seems desirable that an attempt be made to define, and delimit for the purpose of this lecture, the terms primary atypical

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pneumonia and influenza. Primary atypical pneumonia¹ is the designation which will be used in referring to a fairly definite clinical syndrome the chief manifestations of which are the result of infection of the respiratory tract. Pulmonary consolidation in varying degree characteristically develops. The condition is thought to be an infectious disease but is not yet attributable to recognized infectious agents, either microbial or viral, of definitely established pathogenicity for man. It occurs more frequently than any other form of pneumonia but usually is not a serious illness and is only rarely fatal.

Influenza is the designation which will be used in referring to a group of specific infectious diseases of established viral etiology. The illness is characterized by symptoms which are predominantly constitutional, although the infectious process is strictly limited to the respiratory tract. Except in rare instances, pulmonary consolidation does not develop. It tends to occur in epidemic form and there are two specific and distinct etiological types which now are recognized. One, termed influenza A, is caused by infection with influenza A virus; the other, termed influenza B, is caused by infection with influenza B virus.² In this discussion no attempt will be made to consider other clinical entities which closely resemble influenza but apparently are different from it as, for example, so-called sporadic grippe or endemic influenza and other undifferentiated acute respiratory diseases.

DIAGNOSIS

During the past ten years there have been unusual opportunities to study a considerable number of patients with primary atypical pneumonia³⁻⁶ and an even larger number with influenza.⁷⁻¹² An attempt has been made to analyze the frequency with which various symptoms and abnormal physical signs occur in patients with these two different illnesses. It was hoped that it might be possible to arrive at means whereby the two conditions could be clearly differentiated from each other on the basis of their clinical manifestations alone. As will be seen this is not always an easy differentiation. Throughout this discussion data relative to atypical pneumonia and influenza will be presented in juxtaposition so that a direct comparison may be made between them.

In Table I is shown the percentage incidence of each of the various symptoms encountered in 50 per cent or more of patients with either

TABLE I

SYMPTOMS PRESENT IN 50 PER CENT OR MORE OF PATIENTS

Symptom	<i>Primary atypical pneumonia*</i>	<i>Influenza**</i>
	<i>Per cent</i>	<i>Per cent</i>
Headache	65	58
Chills or chilliness	59	52
Malaise	61	45
Cough	98	70
Sputum	82	30

* Reference 6

** Reference 10

TABLE II

PHYSICAL SIGNS PRESENT IN 50 PER CENT OR MORE OF PATIENTS

Physical sign	<i>Primary atypical pneumonia*</i>	<i>Influenza**</i>
	<i>Per cent</i>	<i>Per cent</i>
Increased temperature	95	99
Nasal congestion	57	73
Pharyngitis, mild	69	96
Pulmonary signs (indefinite)	99	64
Dullness (slight)	54	13
Altered breath sounds	70	13
Râles (fine)	93	50
Bradycardia, relative	68	30

* Reference 6

** References 7 and 10

atypical pneumonia⁶ or influenza.¹⁰ It will be noted that there are only five such symptoms and that three of these, i.e., headache, chills or chilliness, and malaise, occur with approximately similar frequencies in both illnesses. Cough, however, is much more common in atypical pneumonia than in influenza. Cough is almost invariably present in atypical pneumonia; in the absence of this symptom the diagnosis should be questioned.^{4, 6} In atypical pneumonia cough is usually a

severe symptom and most patients state that it causes more discomfort than any other symptom. Although cough occurs commonly in influenza, it is seldom distressing and usually is not very striking. The production of sputum also is much more common in atypical pneumonia than in influenza. Most patients with the former condition produce considerable quantities of mucoid or mucopurulent sputum; in influenza the amount of sputum is scanty. It appears that on the basis solely of the symptoms which are present in the majority of patients with either illness, only the frequency of a harassing cough and the production of sputum are helpful in differentiating atypical pneumonia from influenza.

In Table II the percentage incidence of various abnormal physical signs present in 50 per cent or more of patients with either of the two conditions is shown.^{6, 7, 10} It will be seen that there are only seven such physical signs. In both illnesses fever is almost invariably present. Nasal congestion is common in both, although slightly more so in influenza. Mild pharyngitis is almost always present in influenza but also occurs in at least two-thirds of patients with atypical pneumonia. If very careful physical examination of the chest is carried out, somewhat abnormal physical signs are found in nearly every patient with atypical pneumonia, and certain abnormal signs are present in almost two-thirds of patients with influenza. The most common finding in either malady is fine moist rales. They are present in nearly every patient with atypical pneumonia and are present, although considerably less definite, in about one-half of patients with influenza. Altered breath sounds, usually rough or harsh, are heard in over two-thirds of patients with atypical pneumonia but only in about one patient in ten with influenza. Slight dullness is elicited in over 50 per cent of patients with atypical pneumonia but only in about 13 per cent of patients with influenza. A pulse rate slower than would be expected from the temperature is commonly present in atypical pneumonia and also occurs in almost one-third of patients with influenza. In general, relative bradycardia is somewhat more striking in the former condition than in the latter. Apparently there are no pathognomonic signs which clearly distinguish between atypical pneumonia and influenza, although the frequency with which indefinite signs are found over the chest in the former condition is considerably greater than in the latter.

In Table III are presented certain distinguishing features which are helpful in differentiating between these two conditions. Atypical pneu-

TABLE III
DISTINGUISHING FEATURES

<i>Observation</i>	<i>Primary atypical pneumonia*</i>	<i>Influenza**</i>
Season	All months	Dec. to Mar.
Occurrence	Sporadic	Epidemic
Incidence	0.25-1 per cent	5-40 per cent
Incubation period	10-15 days	1-2 days
Onset	Gradual	Abrupt
Maximum temperature	3rd-6th day	1st-2nd day
" "	102-104°F.	101-102°F.
Duration of fever	6-10 days	2-3 days
Duration of consolidation by X-ray	8-14 days	—
Leukocyte count	Usually normal	Usually normal
Complications	Rare	Rare

* References 4, 6, 19, 22

** References 7-11

monia occurs sporadically during all months of the year. However, the incidence is somewhat higher during the winter months than at other times. Influenza usually occurs in epidemic form and in this latitude seldom develops except during the winter months between December and March. The incidence of atypical pneumonia seldom exceeds 0.25 to 1 per cent, whereas during epidemics influenza may have an incidence ranging from 5 to as high as 40 per cent. The incubation period of atypical pneumonia ranges between ten and fifteen days, whereas in influenza it is only one or two days. There is an important difference between the character of the onset in these two conditions. In atypical pneumonia symptoms develop gradually and become progressively more definite during the first three or four days of illness. In influenza the onset is commonly abrupt and the patient is most ill on the first and second days of disease. Maximum temperature is present in general between the third and sixth days of disease in atypical pneumonia but in influenza it is found during the first and second days of illness. In the former condition the average maximum temperature ranges between 102 and 104° F., whereas in the latter it

TABLE IV
X-RAY FINDINGS IN PRIMARY ATYPICAL PNEUMONIA

<i>Lobes showing consolidation</i>	<i>Per cent of patients*</i>
Either lower lobe	88.6
Right middle lobe	20.7
Either upper lobe	20.7
One lower lobe only	35.8
Right middle lobe only	2.8
One upper lobe only	8.4
1	47.1
2	35.8
3	7.5
4	3.8
5	5.7

* Reference 6

ranges between 101 and 102° F. In either illness there may be little or much fever. Fever lasts longer in atypical pneumonia than in influenza; in the first instance it persists from six to ten days on the average; in the second, from two to three. The most important distinction between the two illnesses is the fact that all patients with atypical pneumonia show x-ray evidence of pulmonary consolidation, whereas in influenza such evidence is only very rarely found. In atypical pneumonia pulmonary consolidation usually is demonstrable by x-ray throughout a period of eight to fourteen days after onset and with the decline in fever resolution occurs gradually. In both conditions the leukocyte count and pattern is generally within normal limits and complications develop only very rarely.

In Table IV an analysis is shown of the x-ray findings in atypical pneumonia.⁶ Consolidation is most common in one or the other of the lower lobes; almost 90 per cent of patients will show consolidation in one of these areas. The right middle and either of the upper lobes may also show consolidation but only in approximately one patient in five. In less than 50 per cent of patients does the consolidation remain con-

TABLE V
SEROLOGICAL FINDINGS

Significant increase in titer of	<i>Primary atypical pneumonia*</i>		<i>Influenza**</i>
	Per cent	Per cent	Per cent
Cold hemagglutinins	20-80		0
Agglutinins against streptococcus MG	20-80		0
Antibodies against influenza A or B viruses	0		70-95

* References 4, 6, 13

** References 7, 8, 10, 11, 14

fined within a single lobe. No fewer than 35 per cent show consolidation in two lobes and an occasional patient may develop pneumonia in three, four or even all five lobes. Although the x-ray picture is usually different from that seen in bacterial pneumonias, it is very doubtful that a diagnosis of atypical pneumonia can be made on the basis of x-ray evidence alone.¹²

Serological studies are of great aid in reaching a definite diagnosis in the case of either atypical pneumonia or influenza and serve to distinguish clearly between them. In Table V is presented the percentage frequency with which a significant increase in the titer of certain serum components is demonstrable in the two illnesses.^{4, 6, 8, 10, 11, 13, 14} In carrying out serological studies it is very important that two or more serum specimens be obtained from the patient. The first serum specimen should be taken as early as possible in the illness, preferably before the fifth day after onset. If possible, additional serum specimens should be taken at weekly intervals thereafter until four weeks from the onset have passed. If only a single late serum specimen can be obtained it should be taken three weeks after onset. When cold hemagglutination tests are to be performed the blood specimen should not be placed in the refrigerator but should be allowed to clot at room temperature and the serum removed before it is cooled. If this precaution is not observed the component responsible for cold hemagglutination may be absorbed by the patient's erythrocytes and removed with the clot; false negative tests will result. When both acute phase and convalescent sera from each patient are studied, a definite increase in the titer of cold hemagglutinins, i.e., agglutinins which react at refrigerator tem-

perature with human Group O erythrocytes, is found during convalescence in 20 to 80 per cent of patients with atypical pneumonia. There is a direct correlation between the severity or duration of the disease and the frequency with which this reaction is demonstrable.¹³ In influenza a definite increase in the titer of cold hemagglutinins does not develop. Agglutinins against streptococcus MG, i.e., a single serological type of non-hemolytic streptococcus, also develop during atypical pneumonia in 20 to 80 per cent of patients.¹³ In this instance, also, there is a direct correlation between the severity of the disease and the incidence of the antibody response.⁶ In influenza antibodies against this microorganism are not produced. The development of antibodies against either influenza A or B viruses is demonstrable in 70 to 95 per cent of patients with influenza. Such antibodies do not develop during the course of atypical pneumonia.^{4, 6} There is no great difficulty in establishing a definite diagnosis when a significant increase in titer is demonstrated by the procedures listed. But there is serious difficulty in establishing a trustworthy diagnosis in patients with atypical pneumonia who fail to develop either cold hemagglutinins or agglutinins against streptococcus MG. Analysis of the available published data reveals that approximately 50 per cent of patients with the condition fail to show either reaction.¹³ It is this large group of patients with atypical pneumonia which requires most careful study if other specific infectious diseases are to be excluded.

Bacteriological studies of the upper respiratory tract are not particularly helpful in assisting in the diagnosis of either atypical pneumonia or influenza. In both conditions the usual bewildering array of microbial species is commonly obtained. Rarely in either illness is it possible by means of the direct Quellung test to demonstrate the presence of typeable pneumococci in secretions from the respiratory tract; in both conditions type specific pneumococci can be isolated by mouse inoculation from at least two-thirds of patients.^{4, 6, 12}

During recent years and especially during the war, numerous extensive studies have been carried out on the nature and identity of the etiological agents responsible for the two illnesses. Some of the more important conclusions proceeding from these studies are summarized in Table VI. Influenza A virus, which was discovered by Smith, Andrewes and Laidlaw¹⁵ in 1933, is recoverable from the respiratory tract of a large proportion of patients with influenza A, and influenza B

TABLE VI
ETIOLOGICAL DATA

<i>Observation</i>	<i>Primary atypical pneumonia</i>	<i>Influenza</i>	
		<i>A</i>	<i>B</i>
Virus recovered from upper respiratory tract;			
Influenza A virus (1933)*	0	+	0
Influenza B virus (1940)**	0	0	+
Serum antibody response against;			
Influenza A virus	0	+	0
Influenza B virus	0	0	+
Volunteer inoculated in respiratory tract with;			
Filtrates (PAP) (1945)***	+	0	0
Influenza A virus****	0	+	0
Influenza B virus*****	0	0	+

* Reference 15 ** References 16, 17 *** Reference 19

**** Reference 20 ***** Reference 21

virus, which was discovered independently by Magill¹⁶ and Francis¹⁷ in 1940, can be recovered from patients with influenza B. Neither virus is found in the respiratory tract of patients with primary atypical pneumonia.^{4, 6} A number of different infectious agents, each of which may be a virus, have been implicated as possible etiological factors in atypical pneumonia during the last eight years. Because of the peculiar properties of these agents and the low virulence of all of them for laboratory animals, it has been difficult to obtain unequivocal evidence for or against their causal relationship to the illness. The present status of the problem has been reviewed recently.^{13, 18} A specific serum antibody response against influenza A virus occurs in the great majority of patients with influenza A as, too, does a similar antibody response against influenza B virus develop in patients with influenza B. In primary atypical pneumonia there is no antibody response against either type of influenza virus.^{4, 6} The Commission on Acute Respiratory Diseases¹⁹ showed that human volunteers inoculated in the upper respiratory tract with bacteria-free filtrates of throat washings or sputum obtained from patients with atypical pneumonia, develop, in about

25 per cent of instances, a condition which has all of the manifestations of the natural illness. Similarly, volunteers inoculated in the upper respiratory tract either with influenza A²⁰ or B²¹ viruses, develop, in the majority of instances, infections which show all of the manifestations of natural attacks of influenza. It is now clearly established that influenza is caused by either one or the other of two specific viruses. It appears probable, also, that in atypical pneumonia the primary incitant is a filtrable agent, presumably a virus.¹⁹ It is of importance to point out that the agent which initiates atypical pneumonia appears to be distinctly different from and not related to either influenza A or B viruses.

In arriving at a diagnosis of atypical pneumonia the following features seem worthy of additional emphasis: gradual onset, frequency of cough, relative bradycardia, the presence of fever for about one week or more, and definite x-ray evidence of pneumonia, with but slight or indefinite abnormal physical signs over the chest. Approximately 50 per cent of patients develop during the illness positive cold hemagglutination, or positive streptococcus MG agglutination reactions. Such reactions are seldom positive until the second week after onset. Conditions which may closely simulate the illness and require differentiation from it are: psittacosis (or ornithosis), Q fever, various bacterial pneumonias including pneumococcal pneumonia, pulmonary tuberculosis and influenza. In children pneumonia associated with measles or whooping cough may present an analogous picture.

In reaching a diagnosis of influenza the following manifestations are of importance: abrupt onset, constitutional symptoms out of proportion to the physical signs, the presence of fever for two or three days, and the absence of pneumonia on x-ray examination. Either influenza A or B virus is recoverable from throat washings during the acute phase of illness and an antibody response against one or the other virus develops during the infection. Maximum serum antibody titers are found during the second and third weeks after onset. The condition should be distinguished from the common cold, other undifferentiated acute respiratory infections, paranasal sinusitis, atypical pneumonia, etc.

PREVENTION

There are two varieties of control which may be applied in attempts to reduce the incidence of an infectious disease. These are: first non-

TABLE VII
DURATION OF IMMUNITY

<i>Following</i>	<i>Relatively immune against</i>		
	<i>Primary atypical pneumonia*</i>	<i>Influenza**</i>	
	<i>A</i>	<i>B</i>	
<i>months</i>			
An attack of;			
Primary atypical pneumonia . . .	3-12	0	0
Influenza A	0	6-12	0
Influenza B	0	0	6-12
Vaccination with;			
Influenza A virus	0	3-8	0
Influenza B virus	0	0	3-8

* Reference 23

** References 14, 21, 24-30

specific control measures, and second, specific prophylactic measures. In the case of either atypical pneumonia or influenza, non-specific control measures are not of much usefulness and have not been shown to decrease the incidence of the illness. All such measures are directed toward reducing opportunities for contact with the inciting agent. Both atypical pneumonia and influenza develop following the introduction of the appropriate causal agents into the respiratory tract; both are air-borne or droplet infections. Satisfactory means for controlling the spread of air-borne infections in populations living under normal conditions are not available. In both conditions there is evidence that the incidence of disease is in a measure related to the degree of crowding; in schools, camps, military installations, etc., in which there is obvious crowding, the incidence of either illness is highest.^{11, 14, 22} Conversely, both conditions are least common among rural populations and the incidence in urban populations appears to be higher than in rural but lower than in institutional groups.^{19, 11}

Specific prophylactic measures are more valuable in the control of a number of infectious diseases than any others. The possibility of inducing a significant degree of immunity against an infectious disease is largely a function of the extent and duration of the immunity which

follows the natural infection. There is no evidence that artificial immunity against any infectious disease can be induced for a period longer than that of the natural immunity which follows infection. In the great majority of instances, immunization against an infection leads to less complete and less enduring immunity than that which follows the infection itself. As will be seen from the data summarized in Table VII, there is evidence that neither atypical pneumonia nor either type of influenza is followed by persistent immunity. Second attacks of atypical pneumonia have been observed within three to twelve months after the first attack.²³ Moreover, there is no evidence that atypical pneumonia is followed by the development of any increased resistance to influenza. In influenza A, as in influenza B, second attacks have been observed within six to twelve months after the initial infection.^{21, 24} Furthermore, an attack of influenza A does not cause an increase in immunity against influenza B nor does the latter infection result in immunity against the former. Neither type of influenza results in demonstrable resistance against atypical pneumonia. It is not to be expected, therefore, that artificial immunization against any one of these conditions would induce immunity against another or that homologous artificial immunity would persist for a long period. The results of extensive studies carried out during the past six years suggest that the administration of influenza virus vaccine probably does not significantly increase immunity against influenza for periods longer than three to eight months^{14, 21, 25-30} and does not immunize against atypical pneumonia at all.

As was stated earlier, there is no specific prophylactic measure which is useful in increasing resistance to atypical pneumonia. Because of serious defects in present knowledge of the etiological factors it has not been possible to devise an immunizing procedure. With influenza the present situation is more favorable. First attempts to immunize human beings against influenza A were made in 1936.³¹ By 1941 it was shown that a significant degree of immunity against the disease could be induced by means of the subcutaneous injection of vaccine containing influenza A virus.¹⁴ Table VIII shows in summary the results of extensive studies carried out to determine the efficacy of influenza virus vaccine during the past seven years. Very large numbers of persons were included in the groups under study. The data shown were obtained in groups of vaccinated persons the total number of whom was more than 24,000 and in comparable groups of normal persons who

TABLE VIII
EFFICACY OF INFLUENZA VIRUS VACCINE

Year	Epidemic Type	Virus vaccine employed	Incidence of disease		Normal persons	Relative incidence, vaccinated persons
			After vacci- nation	Vacci- nated persons		
			Months	Percent	Percent	
1940-41	Influenza A	Unconc. A	4	5.6	8.3	1/1.5*
1943-44	Influenza A	Cone. A + B	1	2.2	7.1	1/3.2**
1945-46	Influenza B	Cone. A + B	1	0.8	11.2	1/14.0***
1946-47	Influenza A	Cone. A + B	4	7.2	8.1	1/1.1****

* Reference 14

** Reference 32

*** References 33, 34

**** Reference 35

were even more numerous. In the Winter of 1940-41, during an epidemic of influenza A, persons who had been vaccinated four months previously with an unconcentrated influenza A virus preparation showed a significantly reduced incidence of the disease as compared to normal controls.¹⁴ For each case among vaccinated persons there was 1.5 cases among normal persons. During the 1943-44 influenza A epidemic, persons who had been given concentrated influenza A and B virus vaccine showed a more striking degree of immunity against the disease.³² One month after administration of the vaccine there were 3.2 cases among normal persons for each case of influenza among vaccinated persons. In the 1945-46 epidemic of influenza B, the efficacy of the same concentrated virus vaccine again was studied. The reduction in incidence of the disease among vaccinated persons was the most striking yet obtained.^{33, 34} One month after administration of the vaccine there developed among normal persons fourteen cases for each case of influenza among vaccinated persons. These results were encouraging and it was hoped that by means of further improvements in the vaccine even more significant degrees of immunity might be achieved. Unfortunately, in the 1946-47 epidemic of influenza A, an unexpected development arose. Four months after vaccination the incidence of the disease was not significantly lower in vaccinated than among control persons.³⁵ This surprising result raised new problems which are still under intensive study. An explanation for the failure of the vaccine during the 1946-47 epidemic appears to have been obtained. Studies

on strains of virus obtained from this epidemic revealed that they were strikingly different in antigenic composition from the influenza A virus strains present in the vaccine which was used. As a consequence, the immunological response of vaccinated persons was inadequate to give immunity against the strain of virus responsible for the epidemic. This result poses an important and as yet unsolved problem concerning strains included in the vaccine and will necessitate reassessment of the significance of antigenic differences between strains of both influenza A and B viruses. Despite the encouraging results which were obtained during the epidemics of 1943-44 and 1945-46, it should be emphasized once more that the relative immunity which follows the injection of influenza virus vaccine probably is not of very long duration and may not be effective against virus strains which are widely different from those present in the vaccine.

TREATMENT

In both atypical pneumonia and influenza treatment is concerned chiefly with provision of adequate rest, relief of distressing symptoms, supply of adequate fluids and a sufficient diet. There are innumerable nostrums which enjoy varying degrees of relatively unwarranted repute, chiefly because they give a measure of symptomatic relief, but there is no evidence that any of these preparations is able to modify the course of either condition or to shorten their duration. It is very doubtful whether the use of antipyretic drugs is justified or of any benefit. For some years we have made no attempt to influence the fever either in atypical pneumonia or in influenza. Symptoms such as cough, particularly when it is paroxysmal or unduly harassing as not infrequently is the case in atypical pneumonia, require appropriate therapy. Codeine usually is satisfactory and may be used frequently. We have never found it necessary to resort to the use of morphine and there are good reasons for thinking that this important drug should be given with great caution in any acute respiratory infection because of its well known depressive action on the respiratory center.

There are no specific chemotherapeutic agents which are of established usefulness in the therapy of either atypical pneumonia or influenza. Various sulfonamides have been used in large doses in both conditions and have been found uniformly to be without definite effect. Similarly, penicillin, even in large amounts and at frequent intervals,

has not produced any significant modification in the course of either condition. Convalescent human serum has been tried in some instances but with it also the results have not been encouraging.

Complications rarely occur following either influenza or atypical pneumonia and generally are not serious. As a consequence, there seems to be no valid reason for the administration of either sulfonamides or so-called antibiotic agents with a view to preventing their development. In those uncommon instances in which serious secondary bacterial infections do arise, appropriate antimicrobial therapy should be promptly instituted.

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MUTATIONAL PROPHYLAXIS*

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SOME medical men may think that it is going far afield into dubious and exotic biological theorizations to consider the phenomenon of mutation in connection with the subject of public health. Perhaps the word "mutation" will convey to their minds the picture of rare and bizarre monstrosities, such as the armless-legless man, the microcephalic idiot, the lion-faced boy, and other circus wonders. Although most such curiosities have, in fact, arisen as a result of mutation, this is an entirely one-sided and far too narrow view of the phenomenon. Even though the mutant, the individual who exhibits the mutation, does deviate in some way from the preceding and more usual type, which we choose to call the normal in the given respect, nevertheless mutated hereditary determiners, or genes, are so widespread in their incidence that every one of my readers undoubtedly harbors several or many of them, received from more or less distant ancestors, and mostly in largely latent condition, but some attaining some degree of expression in the individual himself.

I. CHARACTERISTICS OF MUTATIONS

Though the mutant may be called "abnormal" in the given respect, if we carefully define our term abnormal as meaning merely the less usual in that respect considered alone, nevertheless the phenomenon of mutation itself, that is, the occurrence of changes which become reproduced in subsequent generations, is in a sense the most normal thing about all living matter, being the property that most basically distinguishes living matter from non-living and that has allowed living matter to develop, in its evolution, all the further peculiarities of its marvelous organization. For, on the modern genetic view of evolution, our entire bodily structure, and that of every other animal and plant, with all its

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complicated physiology and biochemistry, has been built up through hundreds of millions of years by means of a long succession of mutations, probably millions of them in all. The thousands of different kinds of genes which we now contain, and which we call normal genes, co-operate biochemically in most complicated ways in the formation of every bodily organ and characteristic. Since any one of these many genes can mutate again, and can doubtless mutate in various different ways and to various different degrees, you will see that it would not be possible by a few examples even to scratch the surface of the mutational possibilities in man or any other organism. For anything that can be done by the organism in its development or in its later functioning can be undone by means of a mutation, or can be changed in any one of numerous different ways. In a sense, then, a mutation can do anything that life itself can do, or at least can do a little of it. And, as we shall see, it is the little mutational changes that are the more frequent. They are often so little in their effects that we lose sight of them and it would take the most refined methods to reveal them. Nevertheless, even these have great importance, all told. It would be futile and misleading to present examples of them here, inasmuch as they are of kinds without number.

Our whole intricate human organization, then, is built up of a fabric of thousands of different kinds of genes, each of which was a mutant in its day, but which happened to succeed and so is called "normal" by this time. Nevertheless, *it is only the very rare mutation which thus succeeds*. For, after all, mutations are effects of accidents happening to the genes, and it is not to be expected that accidents in this realm, any more than in any other, will often be beneficial. Most of them, then, fail and die out without ever being seen: they are the mute, inglorious mutations. Now to find out what most mutations are really like, it will not do simply to make a search through the population for abnormal forms, because most of the hereditary abnormal types that we would find have actually been in the population for a long time, having arisen many generations ago. Thus they have already been subjected to much picking over and weeding out, only; unlike what one finds among articles in a department store, it is on the whole the better samples that are left. If we would get a view of what most mutations are like, and in what relative frequencies they occur, we must be careful to examine a group of newly arisen mutants, that have not yet had time to be

subjected to culling out by what is called natural selection. This requires very special genetic techniques, not yet applicable to man.

We can most easily get a batch of fresh mutations by taking a type of organism which is easily bred, and irradiating it. There is evidence, however, that substantially similar results are occurring naturally, in most animals and plants, and that man can be no exception. Let us turn, then, to the favorite little objects of the geneticists, fruit flies of the kind called *Drosophila melanogaster*, and give them a heavy irradiation, about 4500 r units ("roentgens"). When we then breed these with untreated flies, or with each other, we ordinarily find that, among the offspring which develop, not one in a hundred will show a conspicuous visible abnormality, though, on searching through thousands we will eventually find a few abnormal types, of varied kinds. Most mutants are not so easily found. For most of them, what we must do is put each of the offspring through special genetic tests. These tests, in the ordinary case, involve two further generations beyond the immediate offspring, or three generations of descendants in all, to get the mutations to come to light. Even then we seldom actually see the effects directly, their visible expression is so small or obscure.

We detect the presence of the mutations indirectly, however, by the absence, in certain families, or by the relatively low frequency of appearance, of certain expected classes of individuals. These are individuals which carry given treated chromosomes, all derived from the very same treated germ cell ancestral to that family, and which carry no homologous, non-treated chromosome, and not even a (homologous) treated chromosome derived from a different germ cell, for this chromosome of different origin would tend to normalize the effect. In such tests, crosses must in the first place have been made between individuals of different stocks, whose chromosomes have been conspicuously differentiated by having contained, to begin with, certain known genes of visibly contrasting effect, such as, in flies, white versus red eyes, or short versus long wings. The corresponding chromosomes of the contrasting individuals crossed should preferably differ, besides, in their gene arrangement, so that the oppositely marked chromosomes cannot interchange parts (or "cross over," as we say) with one another. Thus the visible character serves as a biological tag, or "marker," as we call it, for the whole of a given treated chromosome. Then there must be a special type of breeding, usually a kind of strict inbreeding, following

this first cross, which would allow this tag or marker to show up in a whole group of second or third generation descendants of any given treated germ cell, in a certain expected ratio, such as the Mendelian 1:3. And we must be able to distinguish between the descendants of different germ cells of the original treated individuals; for this purpose there must not have been intercrossing between them but they must have been kept in separate lines of descent.

On such a system of breeding, if a fresh mutation had occurred in a given treated germ cell, in one of the chromosomes that also carried a "marker" gene, those descendant individuals in the resulting second or third generation family which show the given marker will also carry the new mutant gene, unobscured by any dominant normal from elsewhere, and we would therefore be able to see the mutant effect by looking at these specially marked individuals, provided the effect were a visible one at all. About ten times as often as an externally visible effect, however, when flies are used, is the finding that the expected "marked" group of individuals, carrying the given treated chromosome, simply fails to appear, while the other (the non-marked) individuals do appear, our ratio being, we might say, 0:3 instead of the expected 1:3. This means, it has been proved, that the marked individuals were killed before maturity (before we came to look for them) by a so-called "lethal" mutation which had arisen in the chromosome that bore the marker. Different lethals are, of course, most varied in their action, and succeed in making their kill by any one of hundreds of refined physiological methods, few of which have been much studied. But at least 3 or 4 times as frequent even as these lethal cases and therefore 30 or 40 times as frequent as the cases of visible mutations, in flies at least, are those in which the marked class does appear, and looks about as we expected it to, but appears in a lower frequency than 1:3 though not as low as 0:3. This means that some but not all of the marked individuals have died, and we call such a mutation a "*detrimental*" one, although, of course, there is no sharp line between the categories of lethal and detrimental.

Now the action of a number of visible mutations has been studied by special methods, and it is found that in the majority of cases the mutant gene has an effect similar to the normal gene from which it sprang, but is less active in producing this effect, or, sometimes, even fails to produce it at all. Therefore, it is probable that most of the lethal

and detrimental effects simply involve a more or less reduced activity on the part of some one or more of the innumerable biochemical processes of which the organism is constituted, all of which are results of the action of the genes that lie behind them. It will be seen from this that the effects of the mutations must often be similar to effects of given kinds of unfavorable environmental conditions on normal individuals, weakening them in one way or another. But the mutant individual, having been rendered less resistant to the environmental condition in question, is more easily killed by it. Examining the circumstances attending the death of an individual with the detrimental mutation, then, we might have been inclined to ascribe it to environment rather than to heredity, and to have classed the ailment as an induced one. In truth, the death has required the combined action of a relatively unfavorable environment and of the gene.

Summing up all the mutations discovered by the technique previously described after a dose of 4500 r applied to flies, we find that, instead of there being only 1 mutation among over 100 offspring, as appeared at first sight to be true, each one of the treated germ cells actually carried, on the average, between 3 and 4 fresh mutations, if we include visibles, lethals and detrimentals. In the immediate offspring, however, these seldom lower the chances of living very much, because the mutations from one parent are mostly recessive to the normal genes received from the other parent, even if both parents were irradiated. There may well be twice as many mutations as this, or, say 8 per germ cell, because we have not tried to count the lesser detrimentals, those which kill fewer than, say, 20 per cent of individuals containing them, since it needs such large counts to prove their existence.

In untreated material, the spontaneous mutations which occur undoubtedly fall into similar types, with similar relative frequencies, but the total frequency is only about a hundredth as high as after the heavy irradiation. But even this results in one germ cell among something between ten and thirty having a new *spontaneous* mutation in it, in flies, and this, I submit, is quite a sizeable percentage, larger than generally realized.

2. THE EVENTUAL LETHALITY OF MOST MUTATIONS

Now it might be thought that, since such special genetic techniques are required to make us aware of these mutations, most of them would

lie buried, so to speak, and would be practically negligible in their effects on the population. This point of view is, however, entirely fallacious. For, though the mutation seldom shows in the immediate offspring, the change in the gene is a permanent one and the changed gene will tend to go on down to an unlimitedly long succession of future generations, until by chance it happens to meet, in fertilization, with a similar gene derived from the other parent, and then it will produce its effect, or, as we say, "show," even though it is still invisible morphologically in the great majority of cases. If it is a fully lethal mutant, however, the resulting individual must die from its hereditary ailment. On the average, then, each new lethal mutant gene received by an offspring leads eventually to one death on the part of some descendant, or, more strictly speaking, it is a half cause of death, since the death requires a homologous lethal in the other germ cell that enters the combination, but this effect is none-the-less certain to occur in the end anyway. (Geneticists can avoid this complication by saying that each recessive lethal eventually causes the death of one "genome," or single set of genes.)

Now what about a merely detrimental mutation? Suppose it is a detrimental that lowers the chances of survival and further reproduction by only 10 per cent, thus giving a 90 per cent chance of continuance. When this mutation eventually has a chance to "show," as we call it, in some distant generation, by reason of the coming together of two germ cells both carrying the same kind of mutated gene, the individual will usually be able to live and reproduce, even though he will probably be noticeably handicapped in his living. Usually, then, the gene will go on down again and so through another long line of descendants which do not show the mutation, until again two likes come together and it "shows" once more. Inasmuch as the chance of death from this cause is in the given case only one in ten, this procedure will tend to occur again and again, the mutant gene diving under cover, so to speak, after every reappearance until, on the average, it has had a chance to show itself ten times, and then finally it will succeed in causing the death of the individual showing it, or least in preventing that individual from reproducing sufficiently to hand down the gene further, an event which we may describe as "genetic death" in any case. Thus in the long course of previous breeding, ten individuals, on the average, scattered here and there throughout many generations, have "shown" it, and have

probably been hampered by it, but in the last one an effect as disastrous as that of a full lethal was finally brought about. The lethal action then was only postponed in time, not avoided, and the detrimental effect was longer drawn out. Similarly, a detrimental gene giving only a one per cent reduction in the chances of survival would tend to go on down until it had been able to "show" itself in a hundred individuals, on the average, before it finally killed one of them or prevented it from reproducing, and so died out.

This conclusion is very important, because it shows that ultimately every small harmful mutation is just as bad, if not worse, in its final effects on the population, than a fully lethal mutation.* Therefore, to estimate the total number of genetic deaths finally caused by a group of mutations that were produced at some given time, we have to count not only the fully lethal ones but practically all of them, even down to the smallest, and add them together. Since, at present, our data are good only for lethals and near-lethals, and not for the very slightly detrimental ones, we may have to revise our figure for the amount of harm done by mutations considerably upwards in the future, when more data for mutations of small effects become available. This is a field which very much needs to be worked in more than it has been.

3. HOW MUTATIONS ACCUMULATE

It is, of course, of considerable interest to know the length of time it will usually take before the recessive mutations produced at any given moment do have a chance to show, during the course of breeding of an ordinary population where no special genetic technique has been used, and also to know the average number of generations between one showing of a mutant and the next one. This knowledge would be important in allowing us to estimate how much effect to expect in the generations immediately following some widespread exposure, such as that occasioned by the bombing of Hiroshima or Nagasaki.

The answer to these questions will necessarily depend upon the number of such mutations already present in the population. If, for

* The present writer arrived at this conclusion several years ago, through the use of thought presented above. However, at a still earlier date, 1937, Haldane had published a mathematical paper (Amer. Nat. 71: 341) entitled "The effect of variation on fitness," in which the same principle is set out, but direct's stated that: "It does not matter whether the gene is lethal or non-lethal." In either case . . . the loss of fitness to the species depends entirely on the total effect." It could be argued that the same principle is in fact expressed here, although derived from the viewpoint of the total effect on the species rather than on the individual genes. Yet the emphasis in the latter manner seems to have been missed by most geneticists since the present writer who saw the paper at that time.

example, 1 in 100 germ cells in a population contains a given type of mutant gene, then a mutant gene of that kind, just produced by irradiation, has a 1-in-100 chance of meeting its like in the next generation, or in fact in any one generation. So too it will, *on the average*, have to pass through a hundred generations before it shows, and that will also be the interval between one showing and the next one, on the average. I must emphasize the word "average" here because it may, of course, show right away, even though it has only one chance in a hundred of doing so, and it may, on the other hand, pass through a considerably greater number of generations than a hundred before it shows.

Have we now any method of determining this period, by estimating what the frequency of a given recessive mutant gene is likely to be in the population? The answer is, "yes," provided we know the frequency with which the mutation originates and also know how detrimental it has usually been. The accumulation of any given kind of mutation in a natural population is governed by a reaction between two opposite processes, that tend to approach an equilibrium, as in the law of mass action in chemistry. The two opposite processes here are fresh mutation and elimination. The mutant gene accumulates because it is not only inherited after occurring but is, in addition, produced anew with each generation by fresh mutations. This accumulation goes on until so many individuals "show" the mutation, and are then eliminated by reason of its disability, that the rate of its elimination becomes equal to the rate at which it arises by new mutation in any one generation.

Let us consider first a fully lethal gene, which is eliminated on every occasion that it "shows." In the case of such a gene a population which has reached equilibrium for it (as most large populations will have) must contain about as high a proportion of individuals "showing" it (and thus eliminated by it) as the proportion of germ cells in which it arises anew with every generation. This is true even though, for the most part, the really newly arisen examples of this mutation are not the ones which do show it in that generation. As an example, let us suppose that a purely recessive amaurotic idiocy, a condition which is practically certain to lead to genetic death whenever it appears, has arisen by mutation in 1 germ cell in 200,000 in each generation, in a given population. This figure of 1 in 200,000 is a reasonable one for us to assume, since it is not very far from the middle of the range of those mutation

frequencies which have already been ascertained for a number of individual genes, not only as in other organisms, but also in man. Assuming this frequency of its origination by mutation, then, it will have accumulated until about 1 person in 200,000 might be expected to show this trait, for then the rate of its origination will equal that of its elimination (inasmuch as each showing leads to elimination).

Observe, however, that many more than 1 *germ cell* in 200,000 in the population will carry this trait when 1 person in 200,000 shows it. For the chance of an individual showing a recessive trait is dependent upon the chance of both the germ cells which united to make that individual having had the gene for it. And this is equal to the square of the chance that either sperm or egg, considered separately, contained it, if we neglect the usually minor correction occasioned by marriages between relatives. That is, if one egg among a given number, x , had the trait and likewise one sperm among x , then one individual among x^2 would be formed by the meeting of such an egg with such a sperm. Stating the matter in another way, in our given case, where 1 in 200,000 persons have the defect, 1 in the square root of 200,000, or approximately 1 in 448 eggs, and 1 in 448 sperm, will carry the gene in question, after it has accumulated to the equilibrium value at which 1 in 200,000 persons manifest it in the population. From this figure of 1 in 448 germ cells we may deduce that it would on the average take 448 generations, or about 13,000 years, in man, before a given gene for this abnormality, which had arisen by mutation in a given generation, finally came to show itself. And yet despite this lag it would on the average show in one individual in the end, anyway, and would then cause his genetic death.

Let us next consider not a lethal but a merely detrimental mutation, for instance, a relatively slight hereditary anemia, having the same frequency of origin by mutation, i. e., 1 in 200,000. Such a mutation, we can calculate, would get to show considerably sooner, as it would have accumulated to a higher frequency in the population before being eliminated as fast as it arose. Suppose, for instance, that this detrimental lowered survival by 10 per cent, having only a chance of 1 in 10 of being eliminated in an individual who shows it. It is evident that in the case of this mutation, there would be ten times as many individuals showing it in the population as were being eliminated by it. Now since, for equilibrium between origination and elimination, 1 in 200,000 have to

be eliminated in every generation, ten times this or 1 in 20,000 must then be *showing* it. And the square root of 1 in 20,000, or 1 in 141, is the proportion of the germ cells which will then contain the gene for it, in the average equilibrium population. It, then, will on the average have to go down through some 141 generations, or some 4,000 years in man, before it gets a chance to show, after any given occasion at which it originated anew, and this will also be the average length of the interval between one of the showings of this gene and the next one, as it passes along. But even a detrimental giving only a 1 per cent lowering of survival turns out to have an interval of somewhat over 1,000 years. So, for practical purposes, we may say that most of the fully recessive genes that could be detected at all must lie latent for thousands of years. This only makes them the more troublesome to find and deal with, however, and it does not lessen the frequency with which they do finally show, all told, in any given generation, including the present one.

Dominant mutants, of course, do not have these long intervals between showings, though they may often be irregular in their expression, and so they are eliminated more rapidly from the population. However, each dominant does as much harm as each recessive and must eventually lead to a genetic death; in fact it is a full, not a half, cause of death. The number of its showings before the death occurs is, as with recessives, inversely proportional to the amount by which it lowers the chance of survival. But since it is likely that most recessives are not completely so, but do have a certain degree of dominance, they may actually show enough to be eliminated much sooner than our calculations on the basis of pure recessivity would indicate. This too is a subject which needs to be gone into with much greater exactitude than it has thus far, as it will have considerable bearing on our judgments concerning the composition of populations, concerning the average length of time it takes before the effects of mutations are detectible among the descendants of those in whom they took place, and concerning the total amount of harm done in the generations more immediately following the application of a mutagenic agent.

We are now in a position to see why people are commonly burdened with little ailments and weaknesses of a "familial" or hereditary nature, since the smaller the detrimental effect of a mutation the more it tends to accumulate, so as to show in numerous individuals. If 1 in 10 germ

cells contains some new recessive mutation, then one-tenth of the individuals in a population at equilibrium must always be dying genetic deaths from such mutations. But only the small minority of these deaths will be due to fully lethal genes. And for all of those dying a genetic death by reason of a lesser, or detrimental gene, there must be a considerably larger number suffering but not dying from the same ailment. Therefore, the problem of these mutations is really affecting practically every individual directly. Everyone, moreover, is carrying latent in him, heterozygous, a much larger number of these genes than those which he "shows." A calculation which I have made from some data giving results of inbreeding in man, if the data can be trusted, leads to the conclusion that every person on the average contains heterozygotously at least one lethal gene, or a group of genes which in effect act as a lethal together, of such a nature as to kill an individual who has received it from both parents at some time between birth and maturity, and this fails to count duly the lethals which can act at other periods of life.

+ HOW HEALTH PRACTICES AFFECT THE ACCUMULATION

Now to say that a given ailment is hereditary by no means signifies that it cannot be ameliorated or even cured or avoided completely, in the individual who would otherwise show it, by means of suitable treatment or conditions of living. That is, in fact, one of the major sorts of jobs which physicians and all who have to do with people's well being are dealing with in man and which agriculturists are dealing with in cultivated plants and domestic animals. It is even to be considered as one of the major functions of civilization itself. To be sure, the fact that there are thousands of different gene mutations, each working through a series of biochemical reactions somehow different, at least quantitatively, from every other, does not mean that in such work we have to be able to identify each mutation as such and to deal with it entirely specifically, since many are similar in their final effects on the more proximate bodily processes with which the physician, the cultivator, or even the physiologist deal, and so they can be dealt with as a class by means of general procedures. In fact, often by the same procedures as the troubles of purely environmental origin. However, a knowledge of the mode of action of the given gene concerned is often very important in the treatment or prevention of its effects. Hence pathology, physiology, medicine and psychology as well, are destined

to become far more complicated than at present, as they gradually take increasing numbers of these idiosyncrasies more and more into account, and differentiate in a more refined manner between them.

In thus ameliorating or rectifying the effect of a lethal or detrimental mutation, we have of course made it what amounts to a less detrimental mutation. Yet, we have not changed the mutant gene itself, and it will be subject to the same laws of inheritance as before. For nobody who knows anything about the subject gives any credence to the doctrine of inheritance of acquired characters nowadays. In making it a less detrimental mutation, however, we automatically change the rate of its elimination, lessening this, and we correspondingly raise the equilibrium frequency of individuals capable of showing it in the population. If it retains any detrimental effect whatever, as it usually will, each such mutation must still result in a genetic death eventually, but it will linger longer in the population, affecting more individuals before it dies out. It has been explained that, the more reappearances a mutant gene is able to have before it finally dies out, the more abundant, in exact proportion to this, it thereby becomes in the population eventually. And any mutation which has ceased entirely to become a cause of genetic death is bound to accumulate to an unlimited degree in the population, as fresh examples of it arise anew in every generation and are from then on passed along, until at last all the individuals of the population come to have this gene from both their parents, and it has become "established," as geneticists say. (We neglect here reverse mutations, but these would usually be much rarer.) Although such a process takes many thousands of years, its occurrence follows an inescapable genetic law.

We must recognize then that hereditary ills are unlike diseases of other kinds, in that in "curing" one of them today we are creating another case of the same kind for tomorrow. The more success we have, and with the more ailments, the more does mutation take advantage of this to encumber the population with these ailments, for which more and more individuals have to be treated anew in each generation. We have then largely escaped the effects of the ailment (though an artificial limb or other patched up character is seldom as good as a natural one), but only at the expense of continuing to treat a portion of the population which grows ever larger, the more successful our treatment gets to be. Mutation, consolidating her victory, then goes on

to take the next line of our defense. For we have won no permanent respite, as, pressing the attack on the already weakened biological basis, further mutations in the same and other genes now arise to plague it, and these, too, accumulate just in so far as we seem to be successful in parrying them. Offering a finger, we eventually find our hand taken; yielding up the hand, we find the whole arm drawn in, and so on and on. There is no limit to this whatever except the complete disappearance of all normal genes by mutation or loss, and by that time, if it were conceivable, we should virtually be making a completely artificial man. If we should merely stop at any intermediate point, however, we should thereafter be continually compensating on a widespread scale for all those mutations which had been allowed to accumulate up to that point. And yet we should not have solved the problem of further mutations at all, because these would still be coming up anew at very much the same frequency as they had been when we started in with our ameliorative procedures, and we should then have to decide what to do about them, after all, making the decision either to treat them and to let them also accumulate still further, or to stop at that point and say, "Hereafter no new harmful mutation will be allowed, so far as we can help it, to perpetuate itself, even though we will treat the individual for its effects."

Since that day when we make our genetic stand has to come some time anyway, unless we are willing to go all the way to the bottom of the biological hill, is it not evident that the sooner it comes the better? What does this mean? Certainly it does not mean that we should stop trying to find the causes and cures of ailments and impairments, whether hereditary or not, nor that we should slacken in our efforts to save and improve existing humanity wherever we can. But it does mean that it is up to us to try to discover increasingly which ills do have, even in part, a hereditary basis, and that we should try to develop means to discourage the accumulation of these hereditary weaknesses through indiscriminate reproduction. In other words, controlled therapy, prophylaxis, and hygiene, applied to the immediate generation, must be balanced by a certain amount of guidance over reproduction, to prevent the ills from piling up for the future.

For this we should know the total mutation rate more exactly. If, for example, one-tenth of our own germ cells contain mutations which have arisen afresh in the last generation, counting not only the lethals

but even those slightly detrimental, than that is the proportion of individuals who, genetically more defective than the others, should restrain themselves from reproduction in each generation. (There will be more than $1/10$ if some of the mutations are dominant, because of each dominant's counting double as a source of genome death.) But if our genetic diagnosis can be, say, only 50 per cent perfect, then twice the given proportion, or one-fifth, must, on the average, avoid reproduction, in order to achieve such a result. Alternatively, their reproduction might simply be somewhat limited instead of entirely discontinued, but in that case a correspondingly larger proportion of individuals still would have to be involved in this way. That is the elementary genetic arithmetic of the situation, and it is unfortunately quite unavoidable, and independent of ideologies.

It is easy to see that all this calls for the development of our knowledge of human and other genes to a point thousands of miles beyond what it is at present. For since all of us carry defective genes, what we ultimately want to know is, who carries the most and the worst. And for that we need to develop means of recognizing them even in their latent or heterozygous condition since most of those we carry are in that condition. Only a little progress has yet been made in that direction, yet enough to show that the problem is not a hopeless one. Any wise guidance must also weigh the especially good genes against the especially bad ones, for it is often worth putting up with temporary difficulties in order to save things which are unusually precious. That is particularly advisable as a policy because of the fact that in later generations the bad will usually have a chance to separate itself from the good by the laws of hereditary recombination, and it will then be time enough to allow the bad to be discontinued. Thus, the matter of dissuasion from reproduction under some circumstances is also bound up with its encouragement under others, but that is too large a matter for us to go into here now.

It will be seen that not only is a great increase in medical and other human knowledge called for in these connections, but that a great change will be required in social attitudes, both on the part of the public in general, and also of medical men, before our increasing knowledge can beneficially influence reproductive practices. However, it will be useful in the meantime to work toward this situation gradually, by making use of the limited knowledge that we have, as best we can, to

discourage the perpetuation of definitely known hereditary defects, while furthering conditions that lend encouragement to the multiplication of hereditary characters that are clearly valuable. If all this seems unduly vague, this vagueness is merely a measure of our present ignorance of details, and our present unpreparedness. For the mutations are definitely there, and both public and private health measures will certainly cause them to accumulate, until the time when counter-measures of some such sort are taken.

5. THE PRODUCTION AND AVOIDANCE OF MUTATIONS

In the above matters, physicians, educators and administrators cannot take or even advise action which is very far in advance of the community's mores, although it is their duty to lead the way in the necessary reshaping of the mores. However, there is another sort of "mutational prophylaxis" (if I may call it so), which it is clearly within their power and duty to take action in. This concerns itself with measures designed to avoid increasing the frequency with which new mutations occur. Clearly, the more distasteful and difficult it may be to retard the propagation of a mutant gene once it has been brought into existence, the more obligated are we to do what we can to prevent its coming into existence. To be sure, we cannot prevent the so-called "spontaneous" mutations from occurring at all, nor is it probable that means will ever be found for greatly reducing their frequency (short of cold cultures of germ cells protected even from natural radiation!). But what we can do is to take more effective steps to protect the germ plasm of our population from having additional mutations induced in it by penetrating radiation of artificial origin and other mutagenic agents. This means first of all a recognition on the part of the biological and medical community itself that these effects do exist and are of serious consequence, and, secondly, their coöperation in letting the public know about them and in protecting the public from them.

Unfortunately, however, this subject has long been looked at askance by many medical men, especially, even in their most authoritative journals, and they have for instance been advised, in an editorial in the *Journal of the American Medical Association* only a few years ago, to wait until harmful effects could be seen in the offspring of irradiated persons before doing anything about it. We have, however, reviewed the reasons why effects discernible in the immediate offspring are to be

found only with the greatest rarity. I venture to predict that the same largely negative results will be evident even at Hiroshima. And we have seen that in flies, under conditions in which fewer than 1 in 100 offspring of an irradiated parent show a visible mutation, in spite of all this, there may actually be between 3 and 4 lethal or decidedly harmful mutations carried unseen in each offspring, and that on the average each of these must eventually lead, somewhere along the line, if they are allowed to continue breeding, to certain genetic death.

True, we do not know the exact frequency of the mutations produced by a given dose of x-rays in mammals, and that is an important point. It is therefore incumbent upon us to call for the expensive large-scale experimentation which the obtaining of results with this material requires. And yet even the meager experiments already done on mice are enough to show that, as in all the widely different forms of life tested, the effect is produced, and that its frequency here is at least of a similar order of magnitude to that in the flies. And that is sufficient for our present argument that precautions must be taken, and that, in the meantime, we must take them on a quantitative basis similar to that which we would use in flies.

Now in judging the amount of effect we must be guided by the important principle, which has been well established, that the frequency of the mutations induced will be proportional to the total dose of radiation received over an unlimited period of time. It is the total amount actually reaching and absorbed in the tissue that counts, no matter how hard or soft the rays, no matter whether given in the form of concentrated and brief or dilute and protracted, of uninterrupted or of greatly and frequently interrupted treatments. There is then absolutely no threshold dose, unlike what is true of many other biological effects of radiation, and even the most minute dose carries a definite chance of producing mutations—a chance exactly proportional to the size of that dose. That chance, taken by itself, may to be sure be negligible for all practical purposes, but it is no longer negligible if, being repeated a number of times, the total dose thereby becomes important. Just how much is important depends upon our standards. If, as in flies, a total dose of 50 r units, applied to the spermatozoa, results in a mutation frequency about equal to the natural mutation frequency, but added to it, and if this frequency is taken as being about one mutation in 10 to 20 germ cells, then I should hold the effect important. For it would

mean that there is at least a 1 to 20 chance of mutation, and therefore this same chance of an eventual genetic death or half-death somewhere along the line of future descendants if the treated germ cells are used in reproduction. On the other hand, in immature germ cells, a dose about twice as high is perhaps needed to give a mutation frequency equal to this.

Before giving an irradiation which reaches the germ cells, then, the amount of benefit which it confers should be weighed against the risk of harm to some future individual, and if this cannot yet be exactly estimated, then it is high time for this problem to have been duly attacked. More generally, we may say that all the radiation which reaches the germ cells of different individuals treated by any given person should be lumped together by him to see the total number of r units therein comprised. If 100 r units double the natural mutation rate in immature germ cells, and if this is itself a frequency of one mutation in 20 germ cells, then 20 times this, or 2,000 r units, causing a 20 times raising, will, on the average, produce one mutation in each germ cell. Thus this total exposure will be practically certain of leading to a genetic ("genome") death among descendants of persons who reproduce to an average extent thereafter. In other words, if the quantitative relations are as in flies, we should use the radiation with the consideration in mind that every 2,000 r units used that reach immature germ cells which will later function should *in toto* have been beneficial enough in their immediate effects to compensate for one certain genetic death in the future. Of course, a record of the probable amounts of radiation received by the gonads of each exposed individual should also be kept for summation, in our accounting. With the greatly increasing use of radiation both in medicine and in industry and warfare, this consideration assumes much greater importance than it previously had.

In the light of the above, the use of X-rays as a means of either stimulating or temporarily inhibiting ovulation becomes an especially indefensible practice, although at present it has a considerable vogue among so-called specialists, and a dose of 300 r to the ovaries is not considered excessive by them. Radiologists will recognize that on few other occasions is there need for the reproductive organs of people who still may use them to receive much radiation, since they can be screened from all but a minimal amount of radiation very simply, as by means of lead shields, combined with other, more ordinary precautions. In view

of the considerable amount of scattered radiation that often exists, however, and especially of the fact that certain classes of patients are subjected to irradiation again and again, such shielding ought to be a matter of routine, yet it seems seldom to be resorted to. And whenever irradiation of superficial tissues in the region of the gonads seems indicated, Grenz rays, because of their very weak penetration, should be used instead of ordinary X-rays. This practice too is far from common as yet, although arrangements for giving X-rays of the Grenz type need not be expensive. Furthermore, the technicians and radiologists themselves, as well as all those who come frequently into the neighborhood of apparatus for irradiation while it is in action, should be protected by suitable pelvis shields which may of course be hidden. This is a minimal precaution for mutational prophylaxis on the part of operators, but, on the whole, it should be a very effective one. At present many technicians have not even been informed that the danger exists; much less do they protect themselves against it. Turning to another field, we find in modern commercial practice such usages as the indiscriminate and unregulated X-ray fluoroscopy of the feet of prospective customers, including little children, in shoe stores, in positions which undoubtedly allow considerable radiation to reach the gonads. This too is a flagrant example of the kind of dangerous misuse of radiation against which decisive measures should be taken.

It should be mentioned that when mature male germ cells, such as commonly exist in the testis for weeks before their discharge, are subjected to radiation, there is another effect besides that of causing gene mutations: that is, breakage and rearrangement of chromosome parts, chiefly of the type called "translocations." These are known to lead, in mammals (mice) as in other animals, to inherited disturbances in germ cell formation, that pursue a dominant course of heredity in both male and female descendants for an unlimited series of generations. Unfortunately, they would not tend rapidly to die out in man, even though they regularly kill off in utero about half of the embryonic offspring of individuals that inherit such a disturbance. For, unlike "dominant lethals," half the offspring who are *not* killed show the disturbance again, when they become mature, and these would naturally tend to compensate for it by more numerous conceptions. The effect is not readily produced by irradiation of immature germ cells, however. And even in the spermatozoa its frequency of production is

more nearly proportionate to the square of the dose of radiation received than to the dose itself. Thus with low doses, say below 5 r, it becomes negligible (the chance of such an effect in mice being only about 1 in 4,500 germ cells at that dose). However, it only takes about a hundred r units applied to the spermatozoa to result in about 10 per cent of them carrying these changes, in mice. It should, therefore, be mandatory for a man to abstain from acts of reproduction for some two months after his testes have been exposed to any considerable dose of radiation. And abdominal fluoroscopy, it should be borne in mind, commonly results in some 80 r being received in one dose! The effect is also produced, though to a somewhat lesser (not yet well determined) extent, on ovarian cells of any post-natal stage.

It would take us too far afield here to go into the question of to what extent the somatic effects of irradiation, seen in the individual himself, such as sterility, inhibition of growth, necrosis, disturbances in the bone marrow and other blood forming organs, and even cancers and leukemias, may be traceable to mutational effects of the radiation produced in the somatic cells themselves. There is much evidence of this being the case, and if so, we might also class the avoidance of these effects as mutational prophylaxis, confined to the treated generation itself. It is chiefly the studies on genetic effects followed through succeeding generations that have furnished the evidence in question, throwing light on the somatic effects, but we do not have time to go into this matter here.

Neither can we go into the interesting recent findings of the mutagenic effects of mustard gas and related substances by Auerbach and Robson, other than to say that with such chemicals too a policy of mutational prophylaxis is indicated. Recently it has been announced by Strong and by Demerec that some at least of the carcinogenic substances also produce mutations, and Stone and his co-workers have obtained mutations in bacteria by growing them on food materials which had recently been irradiated (an effect since interpreted by them as probably caused by peroxides produced). Fortunately, however, the old claims of such common substances as alcohol, ether and lead having mutagenic effects have failed to obtain confirmation.

Before closing, one important new development affecting mutational prophylaxis must, however, be mentioned. That is, of course, the use of atomic energy, both in war and in peace. The radiations thereby

produced are certainly of the types that give rise to mutations, and they must give rise to them with very nearly the same frequency, for a given number of r units, as in the case of X-rays, as experiments with radium long ago demonstrated. That people who survive the effects of a bomb may have received hundreds of r units, has been shown by their frequent permanent or temporary sterility as well as in other ways. These people then must, all told, have many mutations in their germ cells. Their reproduction, as well as that of the persons somewhat less affected, must be adding to the sum of future human ills. It can readily be estimated that each bomb falling in a highly populous area would probably kill more people scattered throughout future generations than those killed in the generation immediately affected. If many such bombs were used, moreover, an appreciable amount of radioactive dust would undoubtedly get carried around to very distant places and this would tend to cause mutations in people generally. Similar considerations would apply to any future peacetime use of atomic energy and of radioisotopes when it becomes extensive, unless most rigorous precautions are used. Such precautions are in fact being used today in atomic energy installations. They will become extremely difficult and cumbersome to enforce, however, when there is widespread use of radioactive material. It will therefore be up to the medical men, working in coöperation with the administrators, to see to it that adequate precautions continue to be taken.

If a total of 300 r units, though finally recovered from to all appearances, produces an average of something like one mutation in every 3 to 6 immature germ cells (as happens in flies), then if people in general were subject to this in very many repeated generations, it will readily be seen that such a large proportion of the population would eventually die genetic deaths as to result in the dwindling away and probably, at last, the extinction of the human race. Long before that, however, the effect would be catastrophic, for the survivors would be loaded with detrimental weaknesses. Nevertheless, these effects might take hundreds of years or millenia to mature, and by that time it would be too late.

I do not wish to be a scaremonger, and I do not think we will ever come to this juncture, provided we survive atomic warfare in this and the next generation at all. However, any part of the process is bad, and it is our responsibility to try to avoid every individual case of death or

malady, no matter how far in the future, which our negligence might otherwise cause. We cannot do this by neglecting the problem, or by denying the mutational effect. It is one of those things which will go on and become all the more troublesome if, simply because we do not like it, we fail to give it official recognition.

Nevertheless, mutation has been the saving process that has been behind all biological progress, and has brought life to its present estate. Let us then determine that, like fire, and like atomic energy itself, it and its effects must eventually be brought under control, for our own everlasting benefit, rather than to our detriment.

6. SUMMARY

Attention is called to the erroneousness of the popular notion that mutants are ordinarily monstrosities or freaks. The nature of the experimental evidence is reviewed whereby it has been determined that the great majority of mutations produce effects which are invisible in the external morphology although detrimental to a greater or lesser degree by interference of varied kinds with physiological functions, more usually by lessening the degree of activity of one biochemical process or another. Since, at the same time, most mutations are recessive and most populations are already laden with very numerous mutations inherited from the distant past, the demonstration of the production of new mutations and the measurement of their frequency ordinarily requires very special genetic techniques. It is for these reasons that we need hardly expect to discover conspicuous evidences of newly arisen mutations in the offspring of parents who were subjected to radiation even though many such mutations were in fact produced.

It is a major task of public health to attempt by prophylaxis, treatment, and general improvement in the conditions of life, not only to avoid and cure ills that are primarily of external origin but also the very numerous ones which, whether we are aware of it or not, may be brought beyond the threshold of expression or aggravated by inherited physiological weaknesses or deviations. It can be estimated that, without modern treatments, something between a tenth and a twentieth of the population may regularly meet what may be designated as "genetic death," from such causes. At least, that is the most probable estimate of the amount of this effect in flies, and it is not likely that in humans the effect is less. But the great decrease in mortality which has been

achieved in modern times indicates that a considerable proportion of these deaths are today avoided. This leads to a consideration of the principles whereby mutant genes accumulate in a population and it is shown that any interference with their dying out inevitably leads to such genes becoming increasingly numerous as new mutations continue to arise in each succeeding generation. In other words, our compensation for the mutations, by medical and hygienic means, inevitably though very gradually leads to the mutations in their turn compensating for the better conditions of living, so as in the end to bring the population to a condition where it has at least as many new ills as it had before, but is besides maximally engaged in endeavoring constantly to counteract the original ones.

The only way in which such a situation can be corrected, while retaining the advantages of public health measures for any then existent population, is by the conscious guidance of reproduction in such a way that a fraction of the population, comprising those who are burdened with the most numerous detrimental mutations and have the fewest especially valuable genes, abstains from reproduction, even though their own genetic ills may largely have been prevented from expression by reason of special prophylaxis or rectifying procedures. As above mentioned, the most likely size of this fraction is between one-tenth and one-twentieth of the population, and it is in any case equal in amount to the fraction of germ cells having new mutations in any one generation. However, the institution of such eugenic measures cannot be expected before considerable changes are brought about in social attitudes, and particularly not before the problem becomes more widely realized both among medical men and the general public.

While the adoption of effective policies of the above kind seems rather distant, it becomes all the more incumbent upon present practice to do everything possible to avoid the production of more mutations in the population than occur under natural conditions. This means, first of all, a more general recognition of the fact that high-energy radiation does produce mutations, in considerable abundance, even though the effects are not readily discernible, as has been explained. With the increasing medical, industrial and military use of X-rays, it becomes mandatory for radiologists to see to it that their technicians, their patients, they themselves, and even bystanders have their reproductive organs protected from scattered radiation so far as possible, by means

of simple lead screens (which would ordinarily be sufficient), and to refrain from the practice of using such radiation either to stimulate the reproductive organs or to produce a sterility that may be temporary. It must be realized that the mutational effect is proportional to the total dose given, no matter in how fractionated or diluted a form it may have been received. It is, therefore, desirable that a record be kept of the approximate number of exposures and the amount of radiation received by each person from the time of his conception until that of each reproduction on his part. A record should similarly be kept by each practitioner of the total dose to which the gonads of all his patients and operators taken together, who are likely thereafter to reproduce, have been exposed. Finally, it becomes especially important for men exposed to relatively heavy doses to refrain entirely from reproduction for some two months after exposure, on account of the additional danger of the production of chromosome breaks in the mature spermatozoa as these result in "translocations" giving an inherited proclivity to produce aborted embryos.

With the increasing use of atomic energy both in peace and war, the problem must become much more acute, both because the radiation in this case is so much more penetrating that shields are ordinarily quite inadequate, and because the substances producing the radiation may become so pervasive. It will, therefore, be incumbent upon medical men to insist that adequate protective measures are taken. The protective measures now in force in the centers of production of fissionable material are very good, but the difficulties of protection must become inordinately greater with the more abundant and widespread use of such material, in whatever way.

Finally, it is urgent that further research on mammals be instituted, with the object of determining quantitatively the frequency and the distribution of types of mutations produced by given doses of radiation. Only then can we know definitely just what risks of damage and genetic death of individuals of future generations are involved in the exposure of any individual of the present generation to a given amount of radiation, and be able to balance present benefits against future detriments in deciding whether, and how, to resort to a proposed exposure.

SECTION ON MICROBIOLOGY

APRIL 21, 1948

I. EXECUTIVE SESSION

- a. Reading of the Minutes
- b. Nomination of Section Officers and five members of Advisory Board

II. PAPERS OF THE EVENING

AGGLUTINATION OF RED BLOOD CELLS BY VIRUSES

- a. Studies on the nature of red cell agglutination by viruses

George K. Hirst
 Public Health Research Institute
 of the City of New York

- b. The significance of combinations between viruses and host cells

Frank L. Horsfall, Jr.
 Hospital of Rockefeller Institute
 for Medical Research

Gregory Shwartzman
Chairman

Harry Most
Secretary

Studies on the Nature of Red Cell Agglutination by Viruses

GEORGE K. HIRST

Public Health Research Institute of the City of New York

Summary. Some of the facts about the interaction between influenza virus and red cells were reviewed. By testing for the virus adsorbing capacity of red cells, it was found that the virus receptors were very stable to treatment with a number of reagents and to exposure to high temperatures but were inactivated by proteolytic enzymes and by the periodate ion in small concentrations, as well as by influenza virus. These characteristics of the cell receptors were found to be similar to those of the virus inhibitor present in normal serum. Evidence

for the destruction of serum inhibitor by proteolytic enzyme, periodate and by influenza virus was given. Preliminary attempts to isolate the inhibitory principle from normal human plasma yielded a fraction in which the inhibitor activity was destroyed by trypsin, concentrated phenol and by heating. These qualities and the small amount of carbohydrate in active preparations make it seem unlikely that the active principle in serum is closely related to the blood group mucins.

* * *

The Significance of Combinations Between Viruses and Host Cells

FRANK L. HORSFALL, JR., PAUL H. HARDY, JR.,
 and FRED M. DAVENPORT

From the Hospital of The Rockefeller Institute for Medical Research

Combinations between viruses and host cells occur with great frequency. It is very probable that in the absence of such a combination infection with a virus does not develop.

Virus-host cell combinations can be divided, for the purposes of this discussion, into at least three different classes which have various degrees of significance and importance.

These are: 1) contact combinations or virus-cell surface unions, 2) intracellular combinations or virus-cytoplasmic unions, and 3) extracellular combinations or virus-tissue component unions. During the course of infection with a virus these different types of combination are thought to occur in series one after another and in general they appear to occur in the order stated above.

Evidence for the occurrence of combinations between viruses and host cells has been obtained with a number of viruses including some in each of the three chief categories, i.e., so-called bacterial, plant and animal viruses. Because of the apparently constant occurrence of combination, certain workers⁴ now doubt that any virus has been obtained in a state entirely free of contaminating host material. Whether or not such a degree of purification has been achieved is not our present concern. Rather it is the purpose of this discussion to examine some of the evidence concerning the occurrence of combinations between viruses and host cells and to discuss the significance of such unions.

It seems fairly obvious that the first step in infection with a virus probably is contact between the virus particle and a susceptible host cell. This results in one type of contact combination or virus-cell surface union. The adsorption of bacteriophage or bacterial viruses by a susceptible micro-organism provides an excellent example of this type of virus-host cell combination.⁵ Although it seems essential for such a union to occur before infection with a virus can develop, it does not follow that all virus-cell surface combinations result in infection. As an example, heat-killed bacteria combine with bacterial viruses readily but certainly are not infected by them. Moreover, a number of animal viruses combine with erythrocytes as was shown first with influenza viruses,⁶ some even form stable unions,⁷ but none causes infection of the red blood cells. The nature of the cell surface component which unites with a virus has been studied in only a few instances. Evidence has been obtained⁸ which indicates that certain bacterial viruses combine with polysaccharides at the surface of susceptible micro-organisms. There is some evidence⁹ which suggests that certain plant viruses may also combine with com-

plex carbohydrates of the host. In the case of pneumonia virus of mice (PVM) it appears that protein is an essential constituent of the combining component.¹ With influenza virus there is evidence^{8, 9} indicating that the combining component of erythrocytes may be a mucoprotein.

After a virus and a susceptible cell have come in contact and surface combination has occurred, there follows a series of mysterious phenomena about which there is more conjecture than information. It is thought that the virus penetrates the cell membrane and undergoes multiplication intracellularly. With some plant and a number of animal viruses there is good evidence for this point of view. In certain instances the virus actually can be visualized within the cytoplasm of susceptible cells and seen to increase in number. Particularly good examples are provided by the so-called pox virus group which are sufficiently large that their elementary bodies can be seen with a good microscope.¹⁰ Although a virus may become dissociated from cell surface components at the moment it penetrates into the cell cytoplasm, there is no reason to think that it remains uncombined with cytoplasmic components while it occupies an intracellular position. If present concepts regarding the mechanism of virus multiplication are valid, it would appear that in order for sufficient energy to become available for the synthesis of additional virus particles within the cell, the initial virus particle should combine with at least one and probably with a series of intracellular enzymes. Therefore, such virus-cytoplasmic unions appear of decisive importance relative to the possibility of virus multiplication, and would seem to control the process which results in infection. In the light of this concept they are of more fundamental significance than any other type of virus-host cell combination. Very little is known of the nature of intracellular combinations and nothing is known as yet of the intracellular enzyme systems which are required for virus multiplication. So far, almost all frontal approaches to these problems have come up against nearly insurmountable technical difficulties. There appears to be no satisfactory means by which a virus-inaction, so to speak, can be studied. Still it

has been possible to obtain evidence with some plant viruses as well as certain animal viruses which suggests that either polysaccharides or proteins, perhaps both classes of substances, combine with viruses inside susceptible cells. It has been shown¹⁰ that digestion with trypsin releases the aggregates of fowl-pox virus from infected tissue. In trachoma there is evidence¹¹ that the elementary bodies lie in a matrix which is composed largely of carbohydrate and probably is glycogen. Either trypsin or a cellulase obtained from the snail, *Helix aspersa*, liberates tobacco mosaic virus, tomato bushy stunt virus and potato X virus from infected plant leaves.⁶

After a virus has established contact with a susceptible cell and then has undergone multiplication within the cell, numerous virus particles are released or escape from the cell. They may then infect other susceptible cells and repeat the cycle. When virus particles escape from infected cells they may remain combined with cytoplasmic components or may combine with extracellular components, with substances present in the intercellular fluid or with connective tissue cells which in most instances they do not infect. A number of plant viruses become so firmly combined with the fiber of the leaf after release from infected cells that it is virtually impossible to break the union except by rigorous procedures which largely destroy the viruses.¹ Both mumps¹² and influenza viruses¹³ combine with a component present in the allantoic fluid of the chick embryo and it is fairly certain from results recently obtained¹⁴ that such combinations do not dissociate completely. Moreover, it has been shown¹⁵ that influenza virus remains firmly combined with host tissue components even after extensive purification procedures. In the latter instance it is not yet possible to determine whether intracellular, extracellular or both types of combination are responsible for the results obtained. In a few cases there is some indication of the nature of the component which is combined with a virus after it has escaped from an infected cell. With influenza viruses¹⁶ a polysaccharide composed of mannose, galactose and glucosamine units was constantly associated with the purified virus particles and it was thought that host pro-

tein was also present. The results of recent experiments¹⁴ suggest that the combining component in allantoic fluid may be a mucoprotein and in this respect, at least, it seems to be analogous to the erythrocyte receptor which appears to be a mucoprotein.⁹

If virus-host cell combinations occur with the frequency suggested by the results of the studies which have been summarized, it is to be expected that they should lead to peculiar findings, difficult to understand if the existence of such combinations is unrecognized. What has been found with one animal virus is pertinent in this connection.

Normal mice harbor in their lungs a virus which can cause fatal pneumonia in its natural host.¹⁷ The agent is termed pneumonia virus of mice (PVM). The name is misleading because PVM is present not only in mice but also in many other species. It appears that among 9 species of mammals, including man, each is subject to latent infection with the virus¹⁸ and it can cause fatal pneumonia in at least 3 animal species, i.e., mice, hamsters and cotton rats. Among avian species it appears that chickens, as well as chick and duck embryos, do not harbor PVM and are not susceptible to infection.¹

Early investigations¹⁷ showed that the virus is strictly pneumotropic; causes infection of the lungs when given intranasally, but not when given by other routes; stimulates the development of active immunity and is neutralized *in vivo* by immune serum. Complement fixation, however, did not occur in the presence of immune serum and no other *in vitro* test gave positive results with the agent either in the presence or absence of immune serum. Early evidence¹⁷ indicated that the virus was of medium size with dimensions of the order of 100 to 150 millimicrons.

With studies limited by *in vivo* techniques progress was slow and neither the precision nor the quantity of data obtainable was great. This situation changed when it was discovered¹⁹ that PVM causes agglutination of mouse red blood cells. From comprehensive investigations on the hemagglutination phenomenon with the virus there have emerged some unexpected results.^{1, 2, 3, 4}

When fluid and red blood cells are expressed from the cut surface of mouse or

hamster lungs infected with the virus, agglutination of the erythrocytes occurs. Suspensions of such infected lungs do not cause hemagglutination. After heating such suspensions at 70 or 80° C., agglutination of red cells is demonstrable. The addition of material from normal lungs to heated suspensions causes hemagglutination to disappear again but, upon further heating, the property reappears. This cycle of masking and unmasking the capacity to cause hemagglutination can be repeated many times. The virus, although rendered non-infectious, remains otherwise unaltered during the process. These findings led to the concept that stable combination between the virus and a heat labile component of lung tissue was responsible for the results.^{4, 20}

To obtain maximum hemagglutination titers high temperatures are required and the titer is related to both the temperature and time of heating.^{4, 20} Alkali can also be used to unmask hemagglutination with PVM.²¹ To obtain maximum titers a high pH is needed. The virus becomes non-infectious when heated or when mixed with alkali. Consequently, the procedures which unmask hemagglutination also cause inactivation. Until recently it was not possible to cause dissociation of the combination between virus and lung tissue component without destroying infectivity. This has now been accomplished;²² when the electrolyte concentration is sufficiently reduced, free infectious virus dissociates from combination with host tissue. By appropriate variation of the concentration of electrolytes, either combination or dissociation can be caused at will. Of more importance the cycle of combination and dissociation can be repeated many times without causing demonstrable alteration in the combining capacity of either the virus or the host cells.

There is adequate evidence that hemagglutination is caused by free virus particles themselves and not by some other substance in infected lung tissues.²⁰ Free virus can be obtained from infected lungs without subjecting the tissues to grinding.^{21, 23} Such preparations contain infectious PVM in relatively high titer and give, without further treatment, corresponding hemagglutination titers. On the addition of mouse or hamster erythrocytes agglutination occurs

and the virus is carried down with the red cells. Erythrocytes from other mammalian species or from chickens are not agglutinated and the virus is not adsorbed by such red cells.^{4, 20} When particles from the lungs of normal mammals are added to free virus, agglutination does not occur, but the virus sediments along with the lung tissue particles.^{7, 21} Similar particles from tissues other than the lungs of susceptible animals or from chick embryos do not increase the sedimentation rate of the virus.

It is evident that the virus unites with erythrocytes which are agglutinable but does not combine with those which are inagglutinable. Moreover, it also unites with mammalian lung tissue particles but does not combine with particles from other tissues of the same animals or with avian tissues. It is important to emphasize that PVM infects the lungs alone.¹¹ The combination between PVM and erythrocytes or between the virus and lung tissue particles is stable and does not dissociate at physiological electrolyte concentration. When combined with lung tissue particles, the virus is not capable of uniting with red cells or reacting with specific antibody *in vitro* even though it can be neutralized by specific antibody *in vivo*, probably only after the complex has been split.

In intact infected lung tissue much of the virus appears not to be combined; it is infectious and also capable of combining with suitable erythrocytes. When it is uncombined, the virus is capable of reacting with specific antibody *in vitro* and positive reactions are obtained in both complement fixation²⁰ and hemagglutination-inhibition tests.^{20, 21} Free or uncombined PVM is several times smaller than combined virus and is of relatively uniform particle size. Present evidence indicates that the free virus is actually a relatively small agent with dimensions of the order of 40 millimicrons.²¹

In attempts to determine the physical, chemical or immunological properties of a virus, or to estimate the size of the particles, the results will be influenced by the state of the agent. With spherical particles of similar density with dimensions of the order of free PVM (i.e., 40 millimicrons) as compared to combined PVM (i.e., 140 millimicrons), the difference in particle

weight or volume is more than 42 times. Moreover, at least 95 per cent of the particles of combined PVM consist of host constituents distinct and separable from the virus. It is improbable that stable combination with tissue particles is a phenomenon peculiar to PVM alone. As has been indicated, there are reasons for thinking that the phenomenon is not unique and that other viruses behave in a similar manner. Because of this the available data concerning their physical, chemical and immunological properties may require re-evaluation.

The capacity of mammalian lung tissue to combine with PVM appears to be dependent upon a tissue component, not present in other organs, which interacts with the virus.^{1, 22} Only specific antibody possesses greater affinity for the virus than this tissue component.¹ Non-specific adsorption can hardly be invoked as an explanation for combination since suspensions of mammalian tissues other than lung, or of avian tissues, do not bind PVM. Excepting only the red blood cells of mice and hamsters the combining component is present solely in mammalian lungs and is demonstrable in the intact lung.⁷ Since crystalline trypsin, but not other enzymes, destroys the combining capacity of the tissue component, as also do heat and alkali, it is probable that protein is an essential constituent.¹

The available evidence strongly suggests that the combining component in mammalian lungs plays a decisive role in the initiation of infection with PVM.²² The only mammalian organ which can be infected with the virus is that organ which contains a component capable of combining with the virus. Different animal species are susceptible to infection with PVM in different degree.²³ These differences in susceptibility are directly correlated with the quantity of combining component in the lungs of the several species.⁷ It is probable that the first step in the initiation of infection with PVM is combination between free virus and the lung tissue component at the surface of susceptible cells. If this is the case, it may seem paradoxical that combined virus is as infectious as free virus. However, evidence has been obtained

that a substance, probably a proteolytic enzyme, present in the intact lung can split the combination and release free virus which then can combine with and infect susceptible cells.⁷ It appears now that an essential preliminary step in establishing infection with combined virus is splitting of the virus-tissue component complex in order that free virus, so released, may recombine with the component at the surface of susceptible cells in the lung.^{7, 22}

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
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MODERN TREATMENT OF PULMONARY
SUPPURATION*

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BY SUPPURATIVE disease of the lung is meant an infection of the pulmonary parenchyma distinct from the ordinary pneumonias in which a variety of pyogenic organisms as well as the anaerobes of the mouth, notably the spirochaetes and fusiform bacilli, usually take part.

Pulmonary suppuration as the term is usually applied begins as a process pathologically different from pneumonia since all the structures to be found in a given part of the lung are involved. Thus, while in lobar pneumonia only the lumina of the alveoli are involved, in the pneumonitis in which some of the anaerobic mouth organisms participate, the bronchial walls, interstitial tissues, alveolar walls and even the blood vessels may be massively invaded and filled with the products of an intense inflammatory reaction. Moreover, while resolution is the rule in the various pneumonias and without apparent structural damage, the result of pneumonitis is at best a dense fibrotic scarring of the site and at worst the complete destruction of a large portion of the lung by

* Given 12 December 1947 in the Friday Afternoon Lecture Series of The New York Academy of Medicine.

gangrene. This process begins almost always as either a localized area going on to abscess formation or as bronchiectasis, but since unless eradicated completely both these processes tend to undergo recurrent exacerbations, many of the cases of pulmonary suppuration are seen in the later stages and when the pathological changes are far advanced.

Bronchiectasis. Although there may be a considerable amount of variation in the anatomical findings in bronchiectasis, the basic therapeutic problem is much the same in all and is so often best handled by surgical measures that this should be considered as the definitive treatment in all cases, although it may for various reasons be withheld in some. A patient with the characteristic findings of bronchiectasis has a serious condition which is apt to become progressively worse and which carries both a high morbidity and mortality rate. Such patients are prone to develop "pneumonia"—in reality an exacerbation of the basic suppurative process described above—which through recurrences may virtually incapacitate an adult so far as work is concerned and may seriously interfere with the normal growth and education of a child or adolescent.

The diagnosis of bronchiectasis is not difficult, and the demonstration of its extent by carefully performed bronchogram is usually quite successful. It is necessary, however, to be suspicious of its presence whenever a child or adult suffers from repeated chest colds or when a patient has a so-called unresolved pneumonia.

While the etiology of bronchiectasis is still obscure, it would appear that protracted cough or narrowing of the air passages such as is commonly seen in asthma, allergic bronchitis, or in bronchial stenosis from other causes may be definite contributory factors. The upper respiratory tract may be of importance both as a source of the initial infection, and when chronic or acute sinusitis is present may be responsible for repeated recrudescence of the pneumonitis. Elimination or curtailing of these upper respiratory infections is a most important part of the therapy. This becomes more obviously vital when we realize that it can be shown that in many patients with pulmonary suppuration the pharyngeal reflexes are quite sluggish—indeed, some like the gag reflex may be completely absent.

Most cases of bronchiectasis if they are to be handled conservatively really require a sanitarium type of regimen, including general hygienic measures, ample diet and attention to anemia if present. Elimination if

possible of specific sensitivities is advisable in the early stages and the modern anti-histamine drugs such as benadryl, pyribenzamine, etc., may be useful in diminishing the bronchial secretions which early, as an allergic reaction, may contribute to the development of bronchial obstruction and thus participate in the pathogenesis of bronchiectasis. In the later stages, however, little is to be expected from desensitizing, nor in the presence of actual pulmonary suppuration from these specific drugs.

All of us remember the time when the various arsenicals were employed in the hope of controlling the spirochaetes in such infections, and the disappointment which followed. In most welcome contrast, however, is the use of penicillin, particularly in controlling certain of the flora involved in pulmonary suppuration. While it cannot be considered as curative in the established case of bronchiectasis since here irreversible changes in the bronchial wall have already taken place, it is a most vital ancillary method in the control of reinfection and the prevention of further damage. Its administration by aerosol has the advantage of bringing the drug in more direct contact with the intra-bronchial infection and, as it is absorbed, of producing a systemic effect as well. It has been shown repeatedly that satisfactory blood levels can be produced after inhalation even though larger doses may be required than by the intramuscular route. The so-called vaponenefrin nebulizer which produces very small droplets is the most satisfactory method of administration and the dosage recommended by those with the most experience is from 150,000 to 500,000 units made up in physiological saline 50,000 U/cc. from crystalline penicillin and given in three to five inhalations q.d. Such treatment may be expected to produce moderate to marked improvement in about two-thirds of the cases, with disappearance of many gram-positive organisms, but as with the systemic administration of penicillin, relapse is common. It would seem wise, however, in view of the known high incidence of re-exacerbation of both bronchiectasis and lung abscess in the presence of acute upper respiratory infection to initiate such treatment at the first signs of a cold, not with the idea of controlling the virus but of preventing the rekindling of the intrapulmonary process.

In the absence of facilities for aerosol administration, the systemic route may be used where a dosage of 25,000 U. q. 3 hours or of 300,000 U in oil once or twice a day may be expected to bring about

some improvement in the majority of cases. It should be emphasized that penicillin alone seldom if ever cures established bronchiectasis.

When Friedländer's bacillus or gram-negative organisms are present, streptomycin, 0.5 gm. T.I.D., may also be employed with benefit.

Since conservative local measures have as their purpose the elimination of the purulent bronchial secretion by coughing, medication aimed at checking the cough may be harmful while those that promote expectoration are beneficial. The chief conservative measure in the treatment is postural drainage, one of the oldest but still applicable. Many patients are able to select the position best suited for drainage in their own cases, but because of the prevalence of the process in the lower lobes the most satisfactory method is to have the patient lie prone across the bed with the hands on the floor or over the lower part of a hospital bed in which the portion normally supporting the knees has been angulated sharply upward. In some instances patients tolerate this very well and can even sleep in this position. Postural drainage finds its chief usefulness as a preparation for surgery and as a definitive measure in those cases in which because of extensive bilateral involvement or for other reasons operation is inadvisable.

Bronchoscopy should be carried out in all cases, if only to rule out the presence of foreign body or bronchial stenosis, benign or malignant, as possible etiological factors. Aspiration of secretions, and particularly those retained behind piled up granulation tissue, may be possible after the local application of vasoconstrictor drugs. Bronchoscopy should usually be withheld, however, in the presence of surrounding pneumonitis since it is apt to be followed by untoward reactions under such circumstances.

It is now generally accepted that the definitive treatment of bronchiectasis is surgical unless certain contraindications such as the general condition of the patient or the too extensive involvement of both lungs makes surgery impossible. Established bronchiectasis is a serious disease, and Perry and King¹ in following 400 patients showed that over a 12-year period the mortality in the non-surgically treated cases was 26 per cent. Of these who died, 41 per cent did so within five years of the recognized onset of the disease, and only 15 per cent lived more than twenty years. It is of further interest that of the persons developing the disease under ten years of age, only 9 per cent lived to be over forty and in only 15 per cent of the patients in the larger series who

were over forty did the disease begin in the first decade.

Bradshaw, Putney and Clerf² found that among a group of 171 patients who could be followed out of a larger series of 242, 112 were living and 59, or 24.5 per cent, had died of bronchiectasis or its complications. Riggins³ reported a 14 per cent mortality in his series of 85 cases, and Hinshaw and Schmidt⁴ in summarizing various series found that less than 10 per cent of the cases of severe bronchiectasis obtained a satisfactory result from any form of medical treatment. They believe the mortality rate within ten or fifteen years after the disease is discovered to be 30 to 50 per cent.

These figures seem high, and yet the best of them are so far inferior to those following surgery as to make indefinite medical treatment and the withholding of surgical intervention a highly questionable procedure in the absence of very excellent reasons. This is particularly true since the advent of penicillin makes possible the prevention of complications such as empyema and sepsis which were responsible for much of the earlier mortality. All the other surgical measures which were formerly employed such as pneumothorax, phrenicotomy, thoracoplasty, pneumonostomy and so-called cautery pneumonectomy have now been abandoned, leaving the field to lobectomy and pneumonectomy.

Lobectomy or pneumonectomy for bronchiectasis as now practised with adequate pre-operative preparation and postoperative care has lost most of its dangers, and patients who survive the operation are more nearly cured and need not fear recrudescence of the disease when all demonstrable bronchiectasis has been eliminated.

The preparation of such patients for operation involves first the accurate delineation of the site and extent of the process, recognizing that while most often to be found in the lower lobes, the middle lobe on the right and its analogue, the lingula of the left upper lobe, are commonly involved either alone or in conjunction with disease in the lower lobes. The indications for surgery in bronchiectasis so far as the sites of involvement are concerned may be summed up by considering it the treatment of choice for those cases in which the disease is restricted to one lobe only, to the right lower and middle lobes, and to the left lower and the lingula of the left upper. In some cases it is also indicated where all lobes of one lung or one lobe of each lung, or two lobes of one lung and one of the other are involved. Severe or continued hemoptysis is an urgent indication for surgical intervention.

provided the source of the bleeding can be identified, though in bilateral disease this may be difficult even after bronchoscopy.

All patients should have adequate postural drainage for several days before operation, and a thorough attempt should be made by this method to clear the bronchial tree immediately before beginning anesthesia. General anesthesia with intratracheal intubation to permit frequent aspiration of secretions and with that type of agent which will permit the cough reflexes to be most promptly re-established is the method of choice. Our own preference is for pentothal induction, followed by cyclopropane.

The technique of intrahilar dissection with individual ligation of the structures is much to be preferred over the older mass ligation or tourniquet methods, but in certain cases in which the hilus is "frozen" because of fibrotic reaction may not be feasible. When possible, however, it should be carried out as it reduces materially the dangers of complicating empyema and bronchial fistula. The stump in any case should be covered with pleura either by a flap from the operative area or a free graft taken from the chest wall or elsewhere. Transfusion on the operating table should be provided as for any major operative procedure.

The courageous attempts at eradication of bronchiectasis by lobectomy of Lillienthal, Heuer, Sauerbruch, Willy Meyer, and others were attended by a frightful mortality, but thanks to their efforts and those of others, as well as to the advances in the general care of patients before and after major surgical procedures, the risk of lobectomy for bronchiectasis is now materially reduced. Thus, the operative mortality in some of the more recent and larger series is as follows: Churchill in 116 patients had a mortality of 3 per cent; Bradshaw and O'Neil,⁵ 24 patients with one death—4 per cent; Maier,⁶ 64 cases with one death—1.6 per cent; and finally in a series from a single Army hospital in this country⁷ in which to be sure the risks may have been somewhat lower due to the pre-induction screening, 196 lobectomies were performed for this condition with one death. The overall mortality of lobectomy in this condition is therefore well below 5 per cent in competent hands.

When more than one lobe and particularly because of the multiple operations required when more than one side is involved, the risk is definitely greater, but in an otherwise uncomplicated case even this

does not compare with that of an indefinite conservative policy. When both sides are affected, operation is attended by an additional risk in that the patient's convalescence after the first procedure must be carried out in the presence of the remaining existing disease.

Postoperatively such patients receive the care given any major thoracotomy—transfusions, oxygen tent as needed, and the retention of the closed drainage tube inserted at operation so long as it continues to function.

Lung Abscess. A lung abscess begins as a localized area of pneumonitis caused by the varied flora mentioned above, and among which the mouth anaerobes may usually be found. It is not necessary to go into the known facts regarding its etiology nor to discuss the polemic which has raged in the past regarding the route whereby the infecting organisms reach the lung. It is to be hoped, however, that the large proportion of the lung abscesses which formerly followed operations about the nose and throat may be reduced in number through the prophylactic use of penicillin before and after such procedures.

In considering the modern treatment of lung abscesses it should be borne in mind that the final healing of any abscess regardless of site or etiology is accomplished through the fulfillment of three processes which, while they may progress concurrently, are all significant. These are drainage or evacuation of the abscess cavity, its sterilization and finally its obliteration. Applying this to the lung abscess we find that in the early stages if access to the bronchus be sufficient to provide adequate and prompt drainage, the normal body defenses may overcome the infection and the walls of the cavity may collapse to produce its obliteration. As the infection persists, however, the tissue reaction, particularly to certain of the mouth organisms, produces an increasingly dense, fibrous wall which makes collapse more and more difficult. Persistence of the infection may be due in a few instances to a retained foreign body, but is more often caused by poor drainage, and this in turn through blockage of the tributary bronchus by edema, granulation tissue or in some cases by tumor. It is estimated that in from 20 to 35 per cent of lung abscesses the normal processes outlined above will bring about cure, but the remainder show a great tendency to chronicity and it is difficult to determine, except on the basis of large experience and then guardedly, when the natural tendency to healing ceases and the trend to chronicity becomes established. Realization of this fact

long ago led certain surgeons, notably Dr. Harold Neuhof⁸ and Dr. George Heuer,⁹ to adopt a more aggressive attitude toward the surgical drainage of lung abscess, and since the advent of modern antibiotic therapy has reduced its complications in this condition, this attitude is now fairly well accepted as correct. While some are more radical and some less so, most experienced thoracic surgeons now adopt the policy that if signs of spontaneous healing such as diminution of fever, cough and sputum and decrease of the size of the shadow in the x-ray both as it relates to surrounding parenchymal reaction and to the size of the cavity itself are not apparent after two or three weeks of conservative therapy, surgical intervention should be undertaken.

The conservative measures used in the treatment of lung abscess are essentially the same as those employed in bronchiectasis, except that in its initial stages the process may be more acute in the former. Postural drainage, intensive antibiotic therapy and bronchoscopy all find a place in the conservative regimen and have about the same limitations here as in bronchiectasis. The early cases treated by penicillin alone in our own series and that of others demonstrated its usefulness in controlling the spread of pneumonitis and causing the anaerobes and certain other organisms to disappear from the sputum and in bringing about a marked decrease in size of the cavity. As this failed to be completely obliterated, however, re-exacerbation promptly occurred when the penicillin was stopped.

Mention should be made here of abscesses yielding Friedländer bacillus and microaerophilic streptococci, the first of which is usually and the latter often insensitive to penicillin, so that a more radical attitude is advisable from the start. Streptomycin may help to eradicate the Friedländer infection, but control of this streptococcus may be exceedingly difficult. This latter organism in our experience often gives rise to multiple lung abscesses and to associated putrid empyema, and these facts when taken with its frequent resistance to antibiotics makes treatment difficult. Here, particularly, early surgical attack on the abscess is desirable.

The modern treatment of lung abscess seen very early in its course may then be said to consist of conservative measures, including postural drainage, intensive antibiotic therapy and bronchoscopy as indicated, for no longer than from two to four weeks at most, unless the process shows very satisfactory evidence of resolution. Even with such evi-

dence, however, the cavity should be followed to complete obliteration, and if conservative measures alone are used, the patient should be kept on what amounts to a sanitarium regimen, including rest, general hygienic measures and meticulous protection against upper respiratory infections for several months. If not evidently successful in producing a satisfactory trend toward healing, conservative measures should be replaced by surgery—in this case drainage in one or two stages as the circumstances and the experience of the surgeon require.

By such means today uncomplicated lung abscesses can be healed in a far greater number than formerly, but unfortunately many if not most are not yet being treated as early or as vigorously as this ideal regimen would require. Either the abscess is not recognized and hence the treatment is begun relatively late, or if started early conservative measures are continued so long that a complete obliteration of the cavity is not obtained and a chronic abscess is the result.

Chronic lung abscess is characterized not only by the thickened fibrous wall already commented upon, but often by the honey-combing of the surrounding lung parenchyma with other abscesses, the result of repeated spread of the infection. Under such circumstances adequate drainage either via the bronchial tree or to the exterior is practically out of the question and surgical extirpation of the involved lung becomes the only alternative. This procedure was formerly accompanied by a high mortality as it usually has to be done in a debilitated patient, but by the use of general supportive measures, antibiotic therapy and technical advances in the removal of such tissue, one of the brightest chapters in pulmonary surgery is being written.

Since in chronic lung abscess only a portion of a lobe is usually involved, the operation commonly employed is segmental lobectomy. In this procedure the bronchus and vessels to the involved segment are divided and ligated near the hilus and only the portion of pulmonary parenchyma removed which is supplied by that bronchus. In this way, neighboring segments of two lobes may be removed if involved, thereby sparing a considerable amount of normal pulmonary tissue. Just as a more radical attitude toward early surgical drainage in suitable cases of acute lung abscess has given demonstrably better results, so the use of segmental lobectomy or even complete lobectomy when indicated is bringing about the cure of chronic abscesses and without the prolonged hospitalization which was the best that could previously

have been hoped for. Such extirpation has the advantage also of identifying a malignancy if present and permitting such additional surgery as may be indicated to be undertaken promptly.

As stated earlier, pulmonary suppuration is a serious condition and one may add that it often presents a complicated problem in therapy, but as I hope I have been able to point out, really significant strides are now being made in improving the results. Because of the variegated picture which may be presented both as regards the extent and severity of the lesions in individual cases, more data must be accumulated before the complete significance of the newer methods can be evaluated. In the meantime, the prompt application of the methods now available to each case and the close co-operation of those responsible for their carrying out in following their results will assure the best results and the lowest incidence of complications.

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MEDICAL ASPECTS OF THROMBOPHLEBITIS*

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TH E WORD thrombophlebitis implies occlusion of a vein by a thrombus, and inflammation of the vein itself. Actually the terms phlebothrombosis, thrombophlebitis, and venous thrombosis may be considered synonyms in most instances. While I am aware that some clinicians identify phlebothrombosis as a separate entity from thrombophlebitis, it has been my experience, ordinarily, that I could not accomplish this. Actually differentiation is of insignificant importance. The clinician cannot depend upon a diagnosis of thrombophlebitis to relieve his mind of the fear of pulmonary embolism which is believed to occur less frequently where there is "phlebitis" than where there is only venous thrombosis. These brief statements do not deny that there are two pathologic entities, venous thrombosis with phlebitis and venous thrombosis without phlebitis. They only deny that one can differentiate the two conditions by clinical means in many instances, and they deny that such differentiation would be important ordinarily, even if it were possible. Therefore, we may dispense with confusion in this presentation by considering synonymous the terms, phlebothrombosis, thrombophlebitis and venous thrombosis. For the sake of clarity I shall use the term thrombophlebitis to include all of them.

In general there are two causes of thrombophlebitis, injury to vein wall and changes in the blood. An example of injury to the vein wall is the thrombophlebitis which follows the intravenous injection of irritating solutions such as a hypertonic solution of sodium chloride. An example of thrombophlebitis secondary to changes in the blood is that occurring in polycythemia vera. Actually these statements oversimplify the problem. There are many instances of thrombophlebitis for which the mechanism is not readily apparent. For example, what causes thrombophlebitis following an abdominal operation? Our studies indicate

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clearly that blood flows more slowly in the veins after operation but we do not know that this slowing of flow causes thrombophlebitis. What causes superficial thrombophlebitis of patients who have cancer of the lung, stomach or pancreas? Do these lesions release noxious substances into the blood which provoke thrombophlebitis? There is no answer to these questions.

Moreover there exists considerable uncertainty relative to the diagnosis of thrombophlebitis at times. There is of course no difficulty when a superficial vein has been transformed into a hard inflamed subcutaneous cord or when an entire limb rather quickly becomes edematous and there is visible evidence of collateral venous circulation. But what is one to conclude when a patient who has had a major abdominal operation complains of soreness in the calf? On examination there may be only slight tenderness to pressure over the calf muscles or on dorsi-flexion at the ankle. Does the patient have thrombophlebitis? We presume so, but usually we have no proof. There was hope, for some time, that phlebography might permit an answer to the question just asked. Actually it has limited value in such cases.

It is beyond the scope of this presentation to consider all the kinds of thrombophlebitis. There is no very good classification either on etiologic, geographic or clinical grounds. It is probably wise in this consideration to omit the rare conditions which are extensively considered elsewhere, and consider the more common. Also, it seems wise to try to express a process of thinking when one sees a patient with thrombophlebitis. Perhaps this is best done with questions and answers as follows.

Question—When a physician sees a patient with superficial thrombophlebitis what should he consider to be the cause? Answer—He should determine first whether the vein has been injured by trauma or injection. He should consider phlebitis in varices, for phlebitis occurs commonly in varicose veins probably as a result of destruction of intima, slowing of blood flow and reduced oxygen saturation of blood. He should consider thrombo-angiitis obliterans because superficial thrombophlebitis occurs at some time in the course of 40 per cent of patients with thrombo-angiitis obliterans. When it occurs there is usually also evidence of occlusive arterial disease but thrombophlebitis may precede the clinical evidence of arteritis for many years. The physician must think of polycythemia vera which notoriously provokes both arterial and

venous occlusion. He must think of malignancy, inasmuch as carcinoma of the bronchus, stomach and pancreas is not infrequently the direct cause of venous thrombosis. There may be failure of clinical evidence of malignancy in these areas at this time but at a later date there may be clinical, surgical or anatomic evidence of carcinoma. Lymphoblastoma may also cause superficial phlebitis. Finally, superficial thrombophlebitis may occur without apparent cause; the situation is comparable to tonsillitis, appendicitis and cholecystitis except that a bacterial cause is not commonly apparent in phlebitis.

The treatment of superficial thrombophlebitis is of course the treatment of the cause of it, when that can be determined. Superficial phlebitis itself may require no specific treatment. Indeed, the commonest type of superficial venous thrombosis, that following injection treatment of varices is ordinarily given no specific treatment. It is surprising how inconsistent we are in our attitude toward two kinds of phlebitis in varices, that caused by injection of a sclerosing solution and that occurring spontaneously. When the phlebitis is intentionally provoked the patient is kept active. When phlebitis occurs spontaneously in varices it has been customary to restrict the patient to bed. There is no satisfactory explanation of this inconsistency. One is quite certain that the clot is firmly anchored to the wall in chemical thrombophlebitis; he is not so certain when thrombosis occurs in varices spontaneously. However, pulmonary embolism from superficial thrombophlebitis is very rare.

There are two aspects of superficial phlebitis which deserve special consideration and care. If the thrombosis progresses close to the juncture of the greater or lesser saphenous systems with the femoral or popliteal veins respectively, its progress must be halted either by anticoagulants or by surgical ligation and division. To fail to halt the process of thrombosis may permit extension of it into the femoral or popliteal vein from which it may become detached to cause pulmonary embolism. The second aspect is the possibility of thrombophlebitis of the deep veins associated with superficial phlebitis. If any evidence of this exists it is well to use anticoagulants.

About what should a physician think when he sees a patient with deep thrombophlebitis? Naturally he should think first of the cause of which the three most common are operation, delivery and bed rest as a result of illness of a medical nature. It may result from trauma, from many infectious diseases as, for example, pneumonia and tularemia, from

polycythemia or leukemia or from pregnancy. If none of these or malignancy or thrombo-angiitis obliterans are apparent on careful examination the physician will need to consider that the thrombophlebitis of the deep veins is of the "idiopathic" type.

One treatment of deep thrombophlebitis is, of course, the treatment of its cause if that can be determined. However, there is need for immediate treatment of deep thrombophlebitis, first to prevent pulmonary embolism, second, to restrict the thrombosis to as small an extent as possible in order to lessen as much as possible the chronic venous insufficiency which is an inevitable consequence of venous thrombosis. It manifests itself after recovery of the acute episode by edema, varices, stasis dermatitis and stasis ulceration.

In addition, we are becoming increasingly more aware of the syndrome of acute peripheral circulatory failure, that is, shock, associated with acute venous thrombosis of a leg. We have noted clinically a number of cases of acute venous thrombosis without pulmonary embolism, which have been characterized by cold ashen moist skin, tachycardia, blood pressure which is low or cannot be determined and transitory azotemia; all of the peripheral arteries may be pulseless and anemia may follow the episode. We have as yet, not made essential studies of circulating blood volume but there is clinical evidence of shock similar to that resulting from hemorrhage. We have not measured the actual increase in the volume of a limb affected with acute venous thrombosis but our estimations indicate that large amounts of fluid, perhaps as much as six to ten liters may be trapped in a limb. The syndrome of shock is probably related to the extent and speed of the swelling of the limb. A limb which is rather quickly and progressively involved with venous thrombosis may swell markedly and thus draw from the general circulation a large amount of blood and water. We are not certain that this syndrome, if untreated, would of itself cause death of the patient but that is a possibility. Certainly every patient with acute venous thrombosis should be observed for signs of peripheral circulatory failure. Transfusion may be indicated to restore the circulating blood volume. The entire subject needs careful study. Currently it can be said only to be provocative.

I have arrived now, somewhat circuitously, to the topic of active treatment of thrombophlebitis. It is unfortunate that there is no surgeon to present the case for ligation of veins. I don't believe that indicates

there is no case for ligation of veins. However, I wish to dismiss it with a few sentences. I believe that anticoagulants will do as much or more for patients with thrombophlebitis as ligation of veins will. I prefer anticoagulants to ligation of veins in all cases except when anticoagulants are contraindicated, and when they have not been effective. It is unfortunate, too, that some surgeon or anesthesiologist is not here to present the case for anesthetization of appropriate sympathetic ganglia. I am aware of the statements that this procedure lessens pain, fever, and edema in acute venous thrombosis. In my experience, with rare exceptions, the pain of acute phlebitis requires only aspirin or codeine. Fever is usually mild and certainly not harmful. I have observed little or no effect of anesthetization of sympathetic ganglia on edema. The statement that this procedure lessens the remote consequences of acute venous thrombosis, that is chronic venous insufficiency, seems on very insecure footing. I wish it could be proved to be true. Finally, I believe that elevation of the extremity and the application of warm moist packs has the same physiologic effect on circulation of a limb as sympathetic block and is to be preferred because of its simplicity.

The contribution to the treatment of thrombophlebitis which is of the greatest interest now is treatment with the anticoagulants heparin and dicumarol

Dicumarol is a pure chemical compound which may be recovered from spoiled sweet clover and which has been prepared synthetically. The discovery that it is the agent which causes spoiled sweet clover disease of animals which is characterized by hemorrhage, the determination of its chemical formula, the synthesis of it and other studies by Link and his associates mark an epoch in research which is admirably presented in the Harvey Lectures for 1943-1944. Dicumarol impairs coagulation of the blood, *in vivo*, by depressing the values for prothrombin. When used clinically it has no other significant effect, except that hemorrhage may result when the concentration of prothrombin in the blood is diminished too greatly. Dicumarol is not an ideal anticoagulant because its effect is delayed for one to two days after oral administration, because its effect persists for several days after discontinuance of administration and because judicious use requires the services of skilled and experienced laboratory personnel. Heparin, the only other anticoagulant available for clinical use, has the advantage of quick action (within a few minutes after intravenous injection) and quick cessation of action

(about three hours after injection). A further advantage is that it can be satisfactorily administered without "laboratory control." The disadvantages of use of heparin are the relatively great cost and the need for parenteral administration.

Heparin and dicumarol are not competitors for clinical use; the use of one complements the use of the other. In many instances they should be used together. Heparin should always be used when an anticoagulant effect is needed quickly and when reliable laboratory determination of the value for prothrombin in the blood is not available. Although it may be given by continuous administration, the intravenous injection of 50 mg. of heparin (5 cc. of solution) every four hours has been satisfactory for clinical use. Dicumarol should be used whenever an anticoagulant effect is needed over a period of days, weeks, months or years, provided that there are available reliable determinations of the value for prothrombin in the blood. When both a rapid and a prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously; administration of heparin should be discontinued when dicumarol has produced a satisfactory effect on prothrombin.*

The Dosage of Dicumarol. The amount of dicumarol to be used depends entirely on the value for prothrombin in the blood after the drug has been administered on two successive days. In our studies we have attempted to maintain the values for prothrombin in the blood between 10 per cent and 30 per cent, since our experiences have indicated that significant hemorrhage seldom occurs when the value for prothrombin in the blood is more than 10 per cent and that intravascular thrombosis seldom occurs when the value for prothrombin is less than 30 per cent. It is possible that dicumarol may be administered with satisfactory results if the value for prothrombin in the blood is not reduced as much as we have indicated.

The inexperienced may be confused by the use of the terms "prothrombin time" and "prothrombin percentage"; they do not have the same significance nor do they have a linear relationship. The laboratory should furnish to the clinician a chart by means of which he may convert prothrombin time into prothrombin percentage. According to the technique used at the Mayo Clinic, a normal prothrombin time is 17 to 19 seconds; a prothrombin time of 27 seconds signifies 30 per cent

* When both heparin and dicumarol are used, blood for determination of the values for prothrombin should be drawn not less than three hours after the last injection of heparin, since heparin itself modifies the result of the test for prothrombin.

prothrombin; 35 seconds signifies 20 per cent prothrombin and 58 seconds indicates 10 per cent prothrombin. However, in other institutions where different thromboplastins or techniques are used in the performance of the prothrombin time test, quite different prothrombin times may correspond to values for 100 per cent, 30 per cent, 20 per cent and 10 per cent prothrombin.

Three hundred milligrams of dicumarol are given on the first day and 200 mg. on the second day. On each subsequent day when the prothrombin is more than 20 per cent, 200 mg. are given. On any day when the value for prothrombin is less than 20 per cent, dicumarol is withheld. There are minor variations of this program depending on sensitivity or resistance of a patient's prothrombin to dicumarol.

The Danger of Hemorrhage When Dicumarol Is Used. The sole danger associated with the use of dicumarol is hemorrhage. In our series of 1,983 postoperative cases minor hemorrhage (epistaxis, hematuria and localized ecchymosis) occurred in 3.4 per cent of cases and serious bleeding (from operative wounds or from the gastrointestinal tract) occurred in 1.8 per cent of cases. One may expect minor bleeding in about one of each 25 postoperative cases and serious bleeding in about one of each 50 postoperative cases. There is a great difference between serious bleeding and fatal bleeding. Although marked bleeding from operative wounds occurred about 40 times during the course of treatment of almost 2,000 patients who had undergone operation, death from hemorrhage occurred only twice. Careful study of the records of these two fatalities, reported in detail elsewhere, indicates that the fatal hemorrhage could not definitely be attributed to the effect of dicumarol. However, the two fatalities emphasize the ever-present danger of hemorrhage when dicumarol is used.

The Prevention and Control of Hemorrhage. The best method of preventing hemorrhage is to use dicumarol expertly. Even then, hemorrhage will occur. When epistaxis, hematuria and local ecchymosis are minor we do not ordinarily alter dosage but observe the patient for signs of more extensive bleeding. If bleeding from an operative wound is continued or marked, synthetic vitamin K (menadione bisulfite) should be administered intravenously in amounts of 60 mg. and transfusion of fresh blood should be used to restore the blood that has been lost. The injection of vitamin K can be repeated at two hour intervals, once or twice as needed.

TABLE I

RESULTS OF USE OF ANTICOAGULANTS IN 352 CASES OF POSTOPERATIVE VENOUS THROMBOSIS

	Cases	
	Expected if Anticoagulants had not been used*	Occurred
Subsequent venous thrombosis or pulmonary embolism	88	9†
Fatal pulmonary embolism	20	0

* On the basis of the rates given in the reports of Barker, Nygaard, Walters and Priestley.

† In 3 cases the percentage of prothrombin in the blood was more than 30. In 1 case use of dicumarol had been discontinued and prothrombin was normal.

TABLE II

RESULTS OF PROPHYLACTIC USE OF DICUMAROL IN 832 CASES OF ABDOMINAL HYSTERECTOMY

	Cases	
	Expected if Anticoagulants had not been used	Occurred
Venous thrombosis or pulmonary embolism	33	3*
Fatal pulmonary embolism	6	0

* Minor venous thrombosis.

TABLE III

RESULTS OF ANTICOAGULANT THERAPY IN 329 CASES OF PULMONARY EMBOLISM

	Cases	
	Expected if Anticoagulants had not been used	Occurred
Subsequent venous thrombosis or pulmonary embolism	144	3
Fatal pulmonary embolism	60	1*

* Occurred after prothrombin time had returned to normal.

Contraindications to the Use of Dicumarol. We use dicumarol cautiously or refrain from its use in renal insufficiency, which prolongs and enhances the effect of dicumarol, after operations on the brain or spinal cord, because bleeding in these regions might result in disaster, in blood dyscrasias with increased tendency to bleed because dicumarol will accentuate the tendency to bleed, in ulcerative lesions because of the tendency to bleed, and in nutritional deficiencies or hepatic diseases associated with potential or actual prothrombin deficiency. We doubt whether the use of anticoagulants adds anything to the treatment of subacute bacterial endocarditis and we do not use them in such cases, since the danger of hemorrhage is relatively great.

*Experience in 2,019 Postoperative Cases.** The results of treatment in 352 cases of postoperative venous thrombosis are shown in Table I. In 832 cases of abdominal hysterectomy dicumarol was given prophylactically (Table II) because experience has indicated that in 4 per cent of such instances venous thrombosis occurs following operation; death from pulmonary embolism occurs in 0.7 per cent. In 329 cases of pulmonary embolism after operation anticoagulants were used (Table III). In addition to the cases considered in Tables I, II and III, there were 470 instances in which dicumarol was used prophylactically to prevent pulmonary embolism and venous thrombosis. These were instances in which venous thrombosis or pulmonary embolism had occurred after previous operations or in which the prospects of postoperative venous thrombosis were considered relatively great. Venous thrombosis occurred in two instances: There was no instance of pulmonary embolism.

In 36 additional cases dicumarol was used prophylactically after amputation of a leg because of arteriosclerosis obliterans or thromboangiitis obliterans; there were no vascular complications except that bleeding into the region of amputation occurred in one instance. Unfortunately no figures are available for comparison of results with and without anticoagulants. We can indicate only that dicumarol provided adequate protection against venous thrombosis in these cases.

An over-all consideration of the 1,513 cases presented in Tables I, II, and III indicates that the following results were achieved: 85 patients survived who might have been expected to die had anticoagulants not been used; 250 patients were spared venous thrombosis or non-fatal pul-

* In many instances of pulmonary embolism heparin and dicumarol were used. In most instances of venous thrombosis, dicumarol alone was used. In all instances in which an anticoagulant was used prophylactically, dicumarol only was used.

monary embolism. No great accuracy is claimed for these figures since alternate patients were not treated with and without anticoagulants; the control figures were calculated from experiences before anticoagulants were used. We recognize the deficiency in this method of study but the striking efficiency of anticoagulants in preventing pulmonary embolism and venous thrombosis is nonetheless impressive.

Additional Disadvantages of Anticoagulant Therapy. In considering venous thrombosis and pulmonary embolism there is one most desirable goal: absolute prevention. This has not been achieved. Table II illustrates the point well. Eight hundred thirty-two patients who had undergone abdominal hysterectomy were treated with dicumarol in order to save six lives and in order to prevent venous thrombosis and non-fatal pulmonary embolism in 30 instances. The returns might be considered small. The numerical results are more impressive in cases of venous thrombosis and non-fatal pulmonary embolism; yet it was necessary, in the aggregate, to treat 681 patients in order to save 79 lives and to prevent further venous thrombosis and embolism in 220 instances. We do not belittle these results. We only emphasize our inability to detect the predisposition to venous thrombosis *before it occurs*. Were it possible to designate the patients who would have venous thrombosis *before they had it*, treatment with anticoagulants would be even more productive. There has been a good deal of study on this phase of the problem of venous thrombosis and embolism; some progress has been made on the periphery but the hard core of the problem remains.

Anticoagulants in the Postpartum State. Previous reports indicate that dicumarol may be used safely and with benefit in the treatment and prevention of venous thrombosis following delivery. Indeed the first dose may be administered prophylactically during labor and administration may be continued during the postpartum state without inducing uterine hemorrhage. Dicumarol may appear in the milk of lactating animals to which it is given; indeed baby rats nursing from mothers receiving dicumarol may bleed and die. However, the dose (5 mg. daily) given to the mother rats produced prothrombin deficiency in their blood and caused them to die in six to nine days. The dose administered to the rats was many times greater than that given to patients, if body weight is considered. No conclusions can be drawn from these studies except that if rats are given excessive amounts of dicumarol, their milk may contain sufficient dicumarol to produce profound prothrombin defi-

ciency in nursing young. There is no clinical corollary to this situation.

We have administered heparin and dicumarol or dicumarol alone to 19 postpartum patients, four of whom had pulmonary embolism and 15 of whom had venous thrombosis in the legs. Four of these patients had undergone cesarean section. Treatment was begun as early as the fifth postpartum day to patients who had vaginal delivery and as early as the eleventh day following cesarean section. There was no unusual bleeding although the values for prothrombin in the blood were mostly between 10 per cent and 30 per cent after the third day of treatment. In no instance was there further venous thrombosis or pulmonary embolism. Only two mothers were nursing their babies while they received dicumarol. Repeated studies of the blood of each baby indicated that the values for prothrombin were never reduced significantly; they were consistently between 90 per cent of normal and normal, even when the values for prothrombin in their mothers' blood were between 10 per cent and 30 per cent.

Our studies support the conclusions of previously published reports that anticoagulants may be used after delivery, as needed for the prevention and treatment of pulmonary embolism and venous thrombosis. The problem of prothrombin deficiency of babies induced by dicumarol in mothers' milk cannot be considered wholly settled, although prothrombin deficiency did not occur in our two cases. When dicumarol is given to a mother who is nursing a baby, it is probably the course of wisdom to give the baby vitamin K or to determine values for prothrombin in the baby's blood and to correct any deficiency of prothrombin which may occur.

Experience with Medical Patients. A group of 288 patients who had various kinds of vascular diseases have been given dicumarol as part of their program of medical treatment.¹

Thrombophlebitis.—In this group were 138 patients. The thrombophlebitis was of the idiopathic type (one episode) in 42 cases and of the re-recurrent idiopathic type (several episodes) in 27. In 16 cases the thrombophlebitis followed trauma, in eight it was associated with acute infections, in eight with carcinoma, in five with blood dyscrasias, in four with thrombo-angiitis obliterans and in 11 with miscellaneous conditions which may cause thrombophlebitis. In 17 cases the thrombophlebitis occurred in varices including incompetent greater and lesser saphenous systems.

In 90 cases the thrombophlebitis involved the iliofemoral or deep sural veins or both.

The chief reason for giving dicumarol was to prevent pulmonary embolism and further venous thrombosis. There is no reliable information available as to the incidence of subsequent pulmonary embolism or venous thrombosis among patients who have thrombophlebitis which does not follow operation but it is reasonable to assume that it may be about as high as in the group of patients who have iliofemoral or sural thrombophlebitis following operations.

In this group fatal pulmonary embolism did not occur; two patients had non-fatal pulmonary embolism during adequate prothrombin deficiency. In four cases subsequent venous thrombosis developed. In one of these cases it occurred after the administration of dicumarol had been discontinued because of difficulties in obtaining blood for prothrombin determinations and after the prothrombin value had returned to normal; in another the venous thrombosis occurred when the prothrombin value was greater than 30 per cent. In the two remaining cases there was adequate prothrombin deficiency at the time of the development of the venous thrombosis.

Pulmonary Embolism.—There were 44 patients in this group. The incidence of subsequent pulmonary embolism and venous thrombosis without anticoagulant therapy among medical patients who have iliofemoral or sural thrombophlebitis is unknown but it probably is the same as that noted among patients after operation. In the group of medical patients with pulmonary embolism now being considered, who were treated with dicumarol, there was no subsequent fatal pulmonary embolism or venous thrombosis; one patient had another non-fatal pulmonary embolism when the prothrombin value was between 20 and 30 per cent.

Incidence of Bleeding in 288 Medical Cases.—Two patients bled from the gastrointestinal tract and one had severe subcutaneous bleeding. Treatment was discontinued in all instances. All patients recovered. Minor bleeding (epistaxis, hematuria and petechiae) occurred twice. Treatment was continued in all instances. The incidence of bleeding (1.0 per cent for major bleeding and 0.66 per cent for minor bleeding) was markedly less than the incidence noted in the postoperative cases considered earlier in this presentation.

Conclusions from Experience with Medical Patients. Our experiences

indicate clearly that the anticoagulants are effective in the treatment and prevention of vascular thrombosis of medical patients just as they are effective in the care of postoperative patients with these conditions. Fatal pulmonary embolism can be prevented and venous and arterial thrombosis can be halted in most instances.

Summary of Experience with Anticoagulants. 1) The expert use of the anticoagulants, heparin and dicumarol, has improved tremendously the outlook for patients who have acute vascular thrombosis.

2) An over-all consideration of 1,513 postoperative patients treated with anticoagulants indicated that the following results were achieved: 85 patients survived who would have been expected to die from pulmonary embolism; 250 patients were spared venous thrombosis or non-fatal pulmonary embolism. In 506 additional postoperative cases in which dicumarol was used prophylactically, venous thrombosis occurred in but two instances; there was no pulmonary embolism.

3) A consideration of 288 medical patients indicates that fatal pulmonary embolism was prevented by anticoagulants. Non-fatal pulmonary embolism and venous thrombosis occurred very infrequently.

4) In general, the use of anticoagulants constitutes the greatest contribution to the successful treatment and prevention of intravascular thrombosis and embolism.

The final questions relative to thrombophlebitis are two. How long does the physician continue anticoagulant therapy and what should he do once the acute phase is over? For the purpose of simplification I shall consider only thrombophlebitis of the deep veins. Ordinarily we continue anticoagulant therapy for about 10 days unless there is evidence of progressive venous thrombosis. I am uncertain about ambulation in the presence of acute thrombophlebitis of the deep veins. I know that some physicians advocate ambulation at once. There is danger certainly in keeping patients in bed over a long period of time. On a number of occasions I have had patients, who according to their statements have been kept in bed several months because, as the physician has said, to become active at an earlier period, might endanger the patient's life from pulmonary embolism. This program usually leads to an acute anxiety state, a profound psychoneurosis. Whatever the physician may believe about the possibility of pulmonary embolism, he should never transmit his belief to the patient although it may be wise to discuss the situation with relatives. I believe a median course is advisable as far as

activity is concerned. Usually I recommend ambulation when edema has largely or wholly disappeared.

The final consideration in deep thrombophlebitis is the management when the patient becomes active. This can be stated in two words. Prevent edema! This is accomplished by adequate bandaging. The test of adequacy is whether or not edema occurs when the bandage is worn. Ordinarily, the cloth-elastic bandage known as Ace bandage or tensor bandage is inadequate. The best bandage, by all means, is the pure gum rubber bandage 3 inches wide and 15 feet long. No attempt is made to bandage above the knee. The edema there disappears in time. The bandage is applied in the morning usually over a lisle stocking. If there is much perspiration it is well to change the stocking and re-apply the bandage at noon. Naturally it is not worn at night. I know little advantage to instructing the patient to sit with the leg on a stool or chair or to elevating it while he is in bed. Once every month the patient discards the bandage for one day. If edema occurs the bandage is worn for another month. Many patients can discard the bandage forever within three to six months.

Bandaging after acute deep venous thrombosis is sadly neglected and accounts for the large number of patients who eventually develop varices, stasis dermatitis, and stasis ulceration. It appears unquestionably true that these complications seldom or never occur when the program of bandaging is carried out.

In this presentation I have attempted to present the highlights of acute thrombophlebitis. A good deal of material has been omitted. Also I have repeatedly expressed opinion rather than proved facts. I have done so only because facts are rare in medicine and because my opinions are based on considerable experience with thrombophlebitis.

R E F E R E N C E

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SOME PRELIMINARY OBSERVATIONS ON THE CLINICAL COURSE OF MYASTHENIA GRAVIS BEFORE AND AFTER THYMECTOMY*

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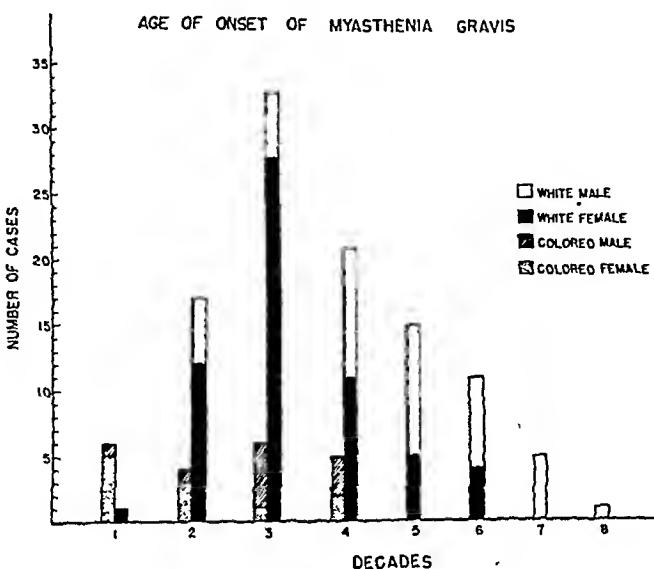
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THE disease myasthenia gravis has attracted the attention of clinical investigators for many years because of its numerous physiological implications. The earliest clinical description of this disease was made by Willis in 1685.¹ In speaking of the various types of palsy he stated: "There is another kind of this disease depending on the scarcity of the spirits in which the motion fails wholly in no part or member yet is performed but weakly only or deprivedly by any. Those who being troubled with the scarcity of spirits, will force them as much as they may to local motions, are able at first rising in the morning to walk, move their arms this way and that or to lift up a weight with strength, but before noon the stores of the spirits which influence the muscle being spent they are scarce able to move hand or foot. I have now a prudent and honest woman in cure who for many years has been obnoxious to this kind of bastard palsy, not only in the limbs but likewise in the tongue. This person for sometime speaks freely and readily enough but after long, hasty or laborious speaking presently she becomes mute as a fish and cannot bring forth a word. Nay, and does not recover the use of her voice until after many minutes."

There are now available accurate methods of measuring neuromuscular function. Many drugs have been found which produce rapid changes in muscle function in these patients, and one is able to make quantitative chemical studies of an enzyme system which has a relation to neuromuscular function. However, there is still very little more of an understanding of the pathogenesis of this disease than when Willis wrote at the conclusion of his description: "The spirits residing in the

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CHART I



brain are conscious of the weakness of the others placed in the members. They refuse to impose local motion on their companions as being a task too difficult for them, for which cause the affected are scarce led by any persuasion."

Myasthenia gravis was thought to be a rare disease until recent advances in diagnosis and treatment became available. These have led to the recognition of an increasing number of cases making possible an evaluation of the natural history of the disease and the situations and circumstances in which it develops. It seems worth while now to review our knowledge of the clinical evolution of this disease for we may find it leads to an understanding of certain relationships between the normal function of the neuromuscular system and of the thymus, relationships which may not emerge from an intense physiological study of an individual case. It is my purpose this evening to describe to you some impressions from the preliminary analysis of 125 cases of myasthenia gravis. Interest has been focussed on the pattern of development of this disease before and after the institution of neostigmine therapy. The results of thymectomy will be reviewed against this background.

The thymus has long been an organ of mystery. Its relationship to myasthenia gravis seems more than coincidental. The results of total

extirpation of the thymus in this abnormality have been variable. Without a more thorough knowledge of the natural course of the disease they cannot be properly evaluated. An understanding of factors responsible for the variable effects of thymectomy may be difficult to obtain. It might transpire that when striking improvement occurred it was merely a spontaneous change and not directly related to removal of the thymus. On the other hand, it is quite possible that such remissions do represent direct effects of the operation. Further, it is possible that failures to improve following operation may have occurred because the disease had reached a stage in its development which precluded a lasting return of muscle power or that a similar situation had been created by the pre-operative treatment. It should also be pointed out that because thymic tissue may be widely scattered complete extirpation may be a very difficult surgical maneuver.

The incidence of this disease with reference to sex and race in relation to age at onset provides some points of interest (*Chart 1*). Of the total of 125 cases 57 per cent were in females, 43 per cent in males; 20 cases or approximately 16 per cent were in Negroes. The disease may begin in any decade of life. The youngest patient in this series was three and the oldest seventy-five years. The distribution by decades was 7 cases in the first, 20 in the second, 39 in the third, 25 in the fourth, 15 in the fifth, 10 in the sixth, 5 in the seventh and 1 in the eighth. It is of some interest that 87 per cent of the female cases began before the age of forty. There was a peak in the incidence among females in the third decade. Following that there was a gradual falling off in the number of cases, none having its onset after the age of fifty-three. There was a more uniform distribution of the cases occurring in males, 56 per cent having their onset below the age of forty, 44 per cent beginning after this age in contrast to only 13 per cent of the cases in females. When one analyzes the cases occurring in the colored race a somewhat similar pattern emerges. In the early age groups there was a predominance in females. It is of considerable interest that none of the cases in Negroes had its onset after the age of thirty-four and that of the cases with onset before the age of ten, six out of seven were in Negroes, only one being of the male sex. It is quite obvious that this analysis must be tentative because of the unrepresentative sampling which may result when patients come from a wide area to a center interested in a particular disease. However, this analysis does confirm clinical

TABLE I

POSSIBLE PRECIPITATING FACTORS ASSOCIATED WITH
THE ONSET OF MYASTHENIA GRAVIS

Acute Upper Respiratory Infection	16
Post-Operative Infection	4
Acute Diarrhea	2
Pyelitis, Acute	2
Tetanus Antitoxin	1
Hyperthyroidism	5
Pregnancy During	1
After Delivery	3
Menstruation	2
Emotional Strain, Severe	4
Electric Shock with Unconsciousness	1
Sun Stroke	1
Carbon Monoxide Poisoning	1
Strenuous Exercise	2

impressions gained over a period of years concerning certain sex and race patterns in relation to the age of onset of myasthenia. In the first decade the typical picture usually is seen in Negro females. In the second and third decades there is a striking predominance of cases in white females while cases in which the onset is late in life characteristically are white males.

It has long been recognized that acute infections, pregnancy, hyperthyroidism and severe emotional tension often precede the onset of this disease. A survey of this series of cases reveals the familiar distribution of these factors associated with the onset of the disease as shown in the accompanying table (Table I).

That sensory disturbances may precede or accompany the first manifestations of weakness is not generally realized. Headache, pain in the eye, numbness and tingling in various regions and other sensory manifestations were described often enough to deserve some consideration. The accompanying table (Table II) shows the incidence of these manifestations in this series of cases. It is worth pointing out that pain

TABLE II
SENSORY DISTURBANCES
AT ONSET

Pain in Eye	5
Numbness and Tingling	
Arms	4
Face	3
Lips	2
Neck	1
Legs	1
Tongue	1
Generalized Paresthesias	2
"Cramps"—Arms and Legs	2

TABLE III
CASES WITH SUDDEN ONSET

Ptosis	10
Diplopia	9
Legs Gave Way	7
Weakness of Mastication	1
Nasal Speech	1
Dysphagia	1
Facial Weakness	1

in the eye led to the diagnosis of aneurysm in two cases resulting in the patients having angiograms and in one instance undergoing a ventriculogram.

Although the onset has been generally described as gradual in cases of this illness, it has been rather impressive in this series that in many instances the first manifestation appeared with such suddenness that the patient was able to date and time the onset very accurately. The accompanying table (Table III) shows the initial symptom in the cases which began precipitately; in the majority of instances ptosis or diplopia appeared first, but it is important to emphasize that the extremities may be the location of the first functional alteration. It is in these cases with dramatic and sudden appearance of symptoms that the diagnosis was not recognized and some vascular abnormality was suspected. The following brief case summaries may serve to illustrate this feature of the disease:

A thirty year old white housewife had acute gastro-enteritis in May, 1939. Ten days later while driving her car she suddenly developed diplopia and drooping of the right lid. She was forced to stop the car on the side of the road and could not proceed until she discovered that double vision vanished when she closed one eye.

The second patient, a sixteen year old white girl, fell suddenly while playing volley ball and could not move her legs for a period of one-half hour. In climbing steps afterwards she noticed extreme weakness of her

TABLE IV

SUMMARY OF INITIAL SYMPTOMS IN MYASTHENIA GRAVIS

Ptosis	Unilateral	- - - - -	28
	Bilateral	- - - - -	15
Diplopia		- - - - -	35
Weakness of legs		- - - - -	18
Generalized Weakness		- - - - -	10
Weakness of Hands, Forearms		- - - - -	9
Dysarthria		- - - - -	12
Dysphagia		- - - - -	9
Difficulty in Mastication		- - - - -	7
Facial Weakness		- - - - -	4
Neck and Shoulder Weakness		- - - - -	2

legs. Several months passed before the next manifestation, ptosis, appeared.

Initial symptoms in this series of cases were similar to those which have been reported previously. The figures in the accompanying table (Table IV), however, show one feature which should be emphasized. This disease may have its first manifestation as weakness of a generalized nature or localized to the arms or legs. It is also worth pointing out that at the onset the involvement may be limited to a very small region. Paresis of one external rectus or the extensor of one finger may be the only recognizable involvement for a long period of time.

In the majority of instances ptosis and diplopia are the first evidence of difficulty. For this reason it seems important here to reemphasize certain characteristic features of the involvement of the eye muscles in this disease. In recent years ophthalmologists have become aware of the unique features of myasthenia of the ocular muscles and many of our cases were first recognized by the eye specialist. Dr. Frank Walsh² has recently analyzed the ocular manifestations in this series of cases of myasthenia gravis and the following points seem worthy of emphasis:

1. Ocular signs or symptoms were present at some time in all cases.
2. Purely ocular myasthenia gravis was observed several times, but in such cases there is always the possibility of spread of the weakness at a later date.

3. Ocular symptoms and signs usually appear early in the course of the disease but occasionally they are a late development.
4. Ptosis is the most common sign.
5. Edema of the lids is a rare prodromal sign.
6. Retraction of the lids is a rare ocular sign which was observed in two cases after ptosis of long standing.
7. The abnormal associated movements of the lids in myasthenia gravis are similar to those resulting from misdirection of regenerated fibers in the third nerve.
8. Weakness of the orbicularis oculi may occur with or without ptosis. Weakness in closure of the lids is overlooked more often than any other common ocular sign.
9. Limitation of ocular movements occurs unilaterally and bilaterally and in almost all combinations.
10. When pupillary abnormalities are present it is doubtful that the case is one of myasthenia gravis.
11. Changes in accommodation were observed in only one case.
12. Visual fields and visual acuity were not altered.
13. The similarity of the ocular signs seen in myasthenia and in hyperthyroidism is worthy of note.

Once the disease has appeared the course may follow a number of patterns. There may be gradual extension of the involved areas leading to a relatively steady state of weakness which, once having reached a level, remains essentially unchanged over a period of years. In the second group there is rapid progress both in the extent of the involvement and its severity, sometimes terminating in death within a very few weeks. In still another type ocular symptoms may be the only evidence of myasthenia over a period of many years. The impression has been gained that patients in this group are predominantly in the later decades.

Since the general recognition of this disease as a separate entity, emphasis has been placed on the tendency for the symptoms to fluctuate in severity and for spontaneous remissions to occur. It is this tendency of the disease to vary in severity from time to time in any one patient that makes any deduction regarding the value of treatment a difficult and delicate matter. Because one of our aims is to evaluate a specific form of treatment in this disease attention will be devoted now to those cases of myasthenia gravis which present a clinical picture of remissions and exacerbations, of which the following is an example:

The patient was a 28 year old white female who entered the hospital in May, 1931, complaining that three weeks previously she had noted the sudden onset of double vision, which gradually increased in severity over a period of three days. Examination at that time revealed weakness of the internal rectus on the left with slight weakness of the facial muscles on the same side. There was moderate ptosis of the left lid. During the next few weeks in the hospital the ptosis and internal rectus palsy were intermittently present. On June 25, 1931 it was noted for the first time that both strabismus and ptosis had vanished. On September 1, 1931 the patient returned to the hospital stating that her previous symptoms had returned and also complaining of fatigue on speaking and swallowing. During the next four years this basic constellation of symptoms was always present. In addition, her illness was characterized by recurrent attacks of generalized weakness with inability to speak or swallow. Often she would choke over her food and at times could not hold objects in her hand. These attacks occurred four to five times a month, lasted for several days at a time, and seemed to be precipitated by exertion. In October, 1935, she contracted an upper respiratory tract infection, her general weakness suddenly became very marked and she could swallow only small amounts of liquids. She could not phonate and had to communicate by writing. On the following day she could take nothing by mouth and began to gasp for breath. At that time she was found to have a temperature of 102°F with evidences of bilateral lobular pneumonia. She was obviously very acutely ill and in marked respiratory distress. There was bilateral ptosis, more marked on the left. Her facial muscles were quite weak and the pharyngeal and palatal movements were absent. She had complete aphonia. There was marked generalized weakness which became rapidly worse with even slight movement. Neostigmine had only been recently introduced at that time. She was given what now would be considered inadequate dosage. There was striking temporary relief, but the effects decreased with subsequent injections and the patient died in spite of artificial respiration.

This sequence of events is fairly representative. The patient had a complete remission lasting for a few months early in the course of her disease. A relapse occurred with involvement of the eyes and pharyngeal muscles. This level of weakness never disappeared after this relapse and the course of the disease was punctuated during the final four years by frequent periods of marked exacerbation of symptoms lasting for a few

days at a time with precipitation of a fatal myasthenic crisis by a respiratory infection.

Kennedy and Moersch in 1937³ published a clinical review of eighty-seven cases of myasthenia gravis and analyzed the remission pattern. They used the term complete remission to describe seemingly total recovery lasting for more than one month and permitting patients to resume their former occupations. A partial remission indicated some improvement lasting for months or years. They did not classify moderate fluctuations of symptoms as a clinical remission. Twenty-seven patients had a total of forty-three complete remissions which ranged from one month to sixteen years. The average duration was 2.2 years, but the majority lasted less than one year. They state that it is quite probable that some of their so-called complete remissions should have been classified as only partial. They found that thirteen patients had seventeen partial remissions which lasted from less than one month to sixteen years, the average duration being 1.5 years, but the majority enduring for less than six months. The duration of the illness in thirty-four patients known to have died varied from six months to twenty-two years, with an average duration of 4.5 years.

Since these cases were all studied prior to the introduction of neostigmine therapy, it is of interest to see what the remission pattern has been in the present series of patients. Essentially the same criteria have been used to define a clinically significant remission. In this series of cases thirty patients have had a remission, twenty-two prior to the administration of any neostigmine and eight during neostigmine therapy. It is of interest to analyze the remissions in patients who were receiving neostigmine therapy. These eight patients had received neostigmine for an average of eight months with a maximum time of thirty-six months and a minimum time of two months. In two of the patients the remission occurred during the few weeks following x-ray therapy to the anterior mediastinum, including the patient who had been on treatment for thirty-six months. If one excludes these two patients, the remaining six had received this drug for a period of five months with a maximum figure of twelve months and a minimum of two.

As a base line for comparison with patients who have undergone thymectomy and will be discussed later, the following figures are of interest. Eight patients had a significant remission lasting from three months to two years. These remissions appeared on an average three

TABLE V

REMISSIONS IN MYASTHENIA GRAVIS
2 YEARS OR OVER

<i>Duration of Remission</i>	<i>Degree</i>	<i>Mo. After Onset Disease</i>	<i>Mo. After Neostigmine</i>	<i>Assoc. Factors</i>
15 yrs.	+++	3	-	—
5 yrs.	+++	24	5	—
5 yrs.	++	1	-	—
4 yrs.	++	24	-	—
5 yrs.	++++	3/4	-	—
4 yrs.	++++	2	-	—
3 yrs.	++++	36	-	—
3 yrs.	+++	1	-	Relapse with pregnancy
3 yrs.	++	1	-	—
2 yrs.	++++	1	-	—

TABLE VI

REMISSIONS IN MYASTHENIA GRAVIS
6 MONTHS TO 2 YEARS

<i>Duration of Remission</i>	<i>Degree</i>	<i>Mo. After Onset Disease</i>	<i>Mo. After Neostigmine</i>	<i>Assoc. Factors</i>
18 mo.	++++	2	2	Symptoms disappeared after pregnancy
14 mo.	+++	3	-	—
12 mo.	+++	3	2	X-ray Thymus
8 mo.	++++	3	3	Neostigmine dosage progressively decreased over 3 months
6 mo.	+++	36	36	X-ray Thymus
4 mo.	+++	5	3	—
4 mo.	+++	1/2	-	—
3 mo.	+++	6	3	Onset followed pregnancy

months after the initial symptom of myasthenia. The longest period being six months and the shortest period two weeks. In nine patients there was a remission lasting from two to fifteen years. In this group the average time after onset of the initial symptom to the development of the remission was eight months. The longest period being thirty-six months and the shortest period three weeks.

The accompanying tables (Tables V and VI) show a more detailed picture of the remission pattern in this group of patients. It will be noted that only one patient had a remission lasting for two years or over after the onset of neostigmine therapy. In this instance the patient was a fifty-five year old male who had predominantly ocular myasthenia. In the group in which symptoms abated for from six months to two years many of the patients had been on neostigmine therapy. All, however, had taken this drug for three months or less with the exception of one case in which the remission developed following x-ray therapy to the thymus. It is of interest that sixty of the 125 patients gave a definite history of having had no significant remissions during the course of their myasthenia.

It is recognized that these data are not sufficiently extensive from which to draw any definite conclusions. However, they do point to certain possible variations in the course of myasthenia before and after the institution of neostigmine therapy. In the early stage of the disease remissions may occur for periods up to at least fifteen years. As the duration of the disease lengthens the probability of a lasting remission of clinical significance grows less. It is also evident that only occasionally does the disease regress once neostigmine therapy has been introduced. The limits of variation, however, are wide, making a definitive evaluation of a procedure like thymectomy extremely difficult. However, the majority of the patients in this series of 125 cases received neostigmine therapy at a fairly early stage in their myasthenia gravis, and it may be of some significance that the most striking remissions and those of longest duration occurred in the relatively small number of patients who had never received any drug treatment.

There is much material of interest in this series of cases regarding factors which influence the intensity of symptoms during the course of this disease. Upper respiratory tract infections almost uniformly result in an exacerbation lasting for a variable period of time. Usually the disease returns to the pre-infection level of severity within a few

days, but occasionally an infection acts as a precipitating factor producing a lasting increase in severity. The onset of the myasthenia in several instances has taken place in a setting of hyperthyroidism, and in at least two cases there has been a very significant reduction in symptoms of myasthenia following thyroidectomy. Pregnancy also influences the course of this disease but the pattern is not always consistent. It has been uniformly true that the disease became more severe following the birth of the child. Menstruation has a very characteristic relationship to the level of symptoms in myasthenia. Almost all female patients will notice an increase in the severity of their weakness for several days before the onset of menstrual flow. After flow begins, either immediately or within a period of a few days there is an abrupt improvement and the female myasthenic feels at her best immediately after the menstrual period. It might be of interest to site an example in which the disease had its clinical onset in relation to the menstrual cycle:

The patient was a forty-two year old white female who became aware in March, 1942 of a peculiar sensation in the facial muscles which she described variously as numbness and twitching. Just before her next menstrual period she noted a generalized feeling of weakness. Following this her menstrual periods became irregular. In October, 1942 just before onset of menstruation the patient developed diplopia and bilateral ptosis. These symptoms disappeared after the menstrual period was over. In January, 1943 again just before menstruation, the patient became aware of difficulty in chewing and was restricted to a liquid diet. This time the symptoms improved after the onset of flow but did not completely disappear. One month later, again just before onset of her period, her speech became involved and she developed generalized weakness.

The influence of infection and menstruation is emphasized as their consistent effect on the course of myasthenic weakness may be of value in estimating the degree of the myasthenic state after thymectomy.

The frequency with which adenoma and hyperplasia of the thymus are encountered in patients with myasthenia has emphasized the possible role played by this organ in the pathogenesis of the disease. In at least one instance prior to 1941 a thymic tumor had been removed following which there was distinct amelioration of the patient's symptoms. It was believed that in order to evaluate the possible relationship of the thymus to the pathogenesis of myasthenia, total extirpation of all thymic tissue should be undertaken in a series of cases. This was begun in 1941 in

TABLE VII
RESULTS OF THYMECTOMY

<i>Group</i>	(1)	(2)	(3)	(4)	(5)
Age (Aver.)	32	29	26	26	38
Sex M	2	1	1	2	4
F	0	5	6	3	2
Mo. Pre-Operative					
Treatment with					
Neostigmine	1	11	29	21	19
Type of					
Thymic Hyperplasia	1	5	6	5	2
Change Thymoma	1	1	1	0	4
Pre-Operative					
Remission (Aver.)	0	One with pregnancy	One partial for 3 yrs. pre-neostigmine	One with preg. pre-neostigmine One for 4 mos. pre-neostigmine	0
Mo. with Myasthenia					
Pre-Operative (Aver.)	17	28	40	47	22
Mo. Post-Operative	79, 34	67, 62, 36,	78, 70, 48, 9,	63, 54, 22, 13, 6	37, 26, 12,
Follow-Up		36, 27, 21	6, 6, 6		6, 6, 5

GROUP (1) = Well

GROUP (2) = Almost well

GROUP (3) = Moderate Return Toward Normal Strength

GROUP (4) = Slight but Continued Improvement

GROUP (5) = Unchanged

collaboration with Alfred Blalock, J. L. Lilienthal, Jr. and F. R. Ford^{4, 5} and since that time thirty-two patients have had their thymus removed. In seven of these a circumscribed tumor was found and in the remaining twenty-five variable amounts of hyperplastic thymic tissue. Three of the patients died in the immediate post-operative period and seven others have died subsequently. All of these patients had a severe form of the disease. Twenty-six have been followed for a period of at least six months since operation. Two patients are well, six have shown an almost complete remission of symptoms, seven have had a partial return of their strength toward normal, five have shown definite but slight and continued improvement and in nine the course of the disease has not changed. The accompanying table (Table VII) shows a more detailed analysis of the results. There are several points of interest. It is well rec-

ognized that the number of cases is too small for reliable analysis, but certain trends are evident which may be of some importance in evaluating the results. In the first two groups which have shown a highly significant degree of remission or complete loss of symptoms pre-operative treatment had been administered for a much shorter period of time than in the groups showing only slight or no remission. The difference in the duration of the disease itself before thymectomy was not striking in the various groups. It is also noteworthy that few of these patients had had any tendency to spontaneous remission in the pre-operative period. It is well to reëmphasize that these patients had a severe form of the disease and most of them were taking large amounts of neostigmine at the time of operation. We have already noted the infrequent appearance of remissions after a patient has been taking this drug for any considerable period of time. Many of the patients were not able to forego neostigmine after operation and this may have lessened the possibility of a post-operative remission. It also may account for the relatively slow time course of the improvement following operation in many of the patients. Of those patients in the first two groups, four now give a definite history that colds no longer influence their muscular strength, and in two of the female patients the characteristic alteration in strength related to the menstrual period has disappeared. In the patients showing little or no improvement, four have shown no change in regard to the influence of infection of the upper respiratory tract on the course of their disease, while six still note the characteristic change in relation to the menstrual period.

In large degree the estimations of improvement have been based on objective changes rather than the alteration in the amount of neostigmine therapy which the patient required. The state of the patient on awakening in the morning, having received no neostigmine during the night, has provided a useful criterion for estimating post-operative improvement. Also some emphasis has been placed on various physical acts which the patient was able to do after operation but not before, with consideration given to the amount of neostigmine being taken in each period.

A summary of the pre- and post-operative neostigmine requirements shows the following facts, the significance of which may be questioned because the attitude of the patient plays a large role in determining the amount which they administer to themselves. In the two patients who

TABLE VIII
DEATHS AFTER THYMECTOMY

No.	Time Mo.	Thymoma	Thymus Autopsy	Post-Operative Improvement	Cause of Death
1	12	+	0	0	Myasthenic Crisis
2	36	+	aberrant nodule neck	+++ (36)	Myasthenic Crisis during dysentery
			++		Sudden relapse
3	5	+	0	0	Myasthenic Crisis
4	6	+	—	+	Myasthenic Crisis
5	6	0	—	0	Myasthenic Crisis
6	40	0	++	++ (12)	Myasthenic Crisis
7	16	0	+	+ (12)	Myasthenic Crisis

Time is in months after operation to death.

In cases 6 and 7 partial improvement lasted for one year. In case 2 for 3 years.

are well, one never had treatment prior to the operation, although his myasthenia was extremely severe, while the other was taking 24 tablets (360 mgm.) in the fourteen hour period when awake. Some years after operation the latter still requires no neostigmine. In the next group with very great improvement the average daily intake pre-operatively was 19 tablets (285 mgm.) and after operation 1.5 tablets (22.5 mgm.). In the next group with only moderate change the intake was 12 tablets (180 mgm.) before and 7 (105 mgm.) after operation, while in the last group with only very slight and questionable change the figures were 11 tablets (165 mgm.) before and 8 (120 mgm.) after thymectomy.

It has been postulated that the thymus gland is the source of a circulating curariform substance which produces the muscular weakness occurring in these patients. Support for this hypothesis was afforded by the clinical observation that in patients with thymoma the disease ran a fairly rapid course with progressive increase in severity. One would expect that in those individuals in whom a distinct thymus tumor was found at operation clinical improvement would be most dramatic. If one charts the deaths which have occurred in patients since thymectomy it is found, as seen in the accompanying table (Table VIII), that most

of them have been, excluding those which occurred in the immediate post-operative period, in those patients from whom a thymoma was removed. It may be noted that with one exception those patients failed to show any real improvement at any time in the post-operative period. One patient operated on within a short time after the onset of the disease and with little treatment before operation had a very satisfactory remission lasting for almost three years. Then, following an infection, she developed an acute exacerbation of myasthenia resulting in death, and at autopsy a nodule of aberrant thymus tissue was found in the neck. In view of the fact that three of the patients from whom a thymoma has been removed have died within the period of one year with no remission one might raise the question as to whether it is advisable to operate when a tumor is demonstrated. In support of this possibility is the following, rather unique, case: The patient, a white female housewife, noted at the age of 39 sudden onset of difficulty in opening the left eye. A few weeks later difficulty in swallowing appeared and on occasions fluids were regurgitated through the nose. The patient could not smile properly and had difficulty in talking. All symptoms were worse late in the day. Examination three months after onset of symptoms showed ptosis of the left lid, a very nasal quality to the voice so that speech was unintelligible and poor movement of the soft palate with essentially normal strength in the extremities. X-rays at that time revealed an abnormal shadow in the region of the aortic arch. The patient was placed on 30 mgm. of neostigmine twice daily and discharged. Two months later she was readmitted following an upper respiratory tract infection during which all of her symptoms had become exaggerated and she was taking 1 tablet of neostigmine every 2 hours. She recovered in a few days and was discharged taking 30 mgm. three times daily. She has been followed up to the present, has shown very little tendency for her disease to progress and rarely takes more than 115 mgm. neostigmine daily. The last x-ray taken on April 14, 1947, nine years after the first detection of a thymic tumor, shows a large mediastinal mass extending from the level of the first rib anteriorly downward to the point where it is hidden by the cardiac shadow. On lateral view the mass is seen to be in the anterior mediastinum superior and anterior to the heart shadow. This patient has had known myasthenia and a probable thymic tumor for nine years with no definite indication of progression of the disease and now is leading a reasonably normal life with the

aid of neostigmine therapy. However, it must be pointed out that of twelve thymic tumors seen in patients with myasthenia gravis in this series of cases three have been malignant with metastases present at the first examination. There is as yet no final answer to the question of whether or not the thymus releases a curariform substance. The weight of the evidence seems against the possibility.

One further comment seems indicated in regard to the post-mortem findings in the patients who have died after thymectomy. In three definite amounts of hyperplastic thymic tissue were found at autopsy. In all three there was a period of remission following operation and then relapse of the disease in the period before death. Only two of the other patients were examined by autopsy and in neither was any thymic tissue discovered. The significance of these observations is difficult to evaluate.

SUMMARY

This preliminary analysis of 125 patients with myasthenia gravis suggests that if significant clinical remissions appear they tend to occur early in the course of the disease. Significant remissions which last for a long period of time appear to be unusual in patients who have received moderate or large amounts of neostigmine for more than six months.

Sufficient data are not yet available to evaluate with finality the effect of thymectomy on the course of myasthenia gravis. Preliminary studies indicate that the beneficial results are greater than one might expect from spontaneous remission in the severity of the myasthenia gravis. This conclusion is further supported by the following: that most of the cases operated upon had very severe myasthenia which had been present for more than six months, that there had been no tendency for the development of remissions pre-operatively, and that large doses of neostigmine had been administered in the pre-operative period and had to be continued for many weeks after operation.

If one may assume that the thymus does play a role in the pathogenesis of myasthenia gravis, the mechanism by which it does so is unknown. Much of present knowledge fails to support the suspicion of the elaboration of a curariform substance by this gland. As a possible clue to the normal function of the thymus an understanding of its role in this disease is important. Long term study of the effect of thymectomy early in the course of myasthenia gravis before prolonged therapy

with neostigimine may reveal information of importance concerning the physiological function of the thymus. The magnitude of this type of clinical experiment is evident when one realizes that spontaneous remission may occasionally last for at least fifteen years.

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THE INFLUENCE OF DISEASE ON HISTORY*

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MAN'S history is a continuous struggle against oblivion. With each succeeding generation he renews the battle, fretted by the inherent urge to dominate his environment and perpetuate himself. In this timeless struggle, man's no less timeless enemies have been war and disease, and of the two, disease is the more insidious, since the weapons against it are the more elusive and imponderable.

So impotent at times has man found himself before this major antagonist, that for long ages he conceived disease as the instrument of a chastising deity. And to appease this Daemonic force, he invoked an entire pantheon of superhuman aids—bodhisatvas, saints and medicine men—to advocate his cause before the supreme rulers. Modern medicine no longer attributes the incursions of disease to the caprices of a too-human deity; it looks closer to man's way of life, to the environment in which he lives, to the human complex, which yields its secrets so reluctantly to the investigator.

This new rationale of disease, however, has not lessened the student's wonder at the extraordinary role of illness in shaping human history. As a protagonist in the drama of man, disease has played hero and villain; effected comedy and tragedy. A tyrant is stricken; a liberator enfeebled; an army contaminated; a people infected—and the denouement is changed!

In a brief sketch such as this, it would be impossible to do justice to the record. It is as long and complex as history itself. In a manner of speaking, it is longer than history itself. For, when the curtain of history rises, earth is already old and its hoary surface is dotted with the traces of man's progenitors. The medical investigator—the paleopathologist—allying himself with the archeologist and the ethnologist, scrutinizes each prehistoric fragment; the relic of Neanderthal man; the mummy of a Pharaoh; the trephanned skull of pre-Colombian man.

* Read before the Section on Historical and Cultural Medicine, The New York Academy of Medicine, January 9, 1946.

From such as these, he learns that no Elysian immunity protected prehistoric man or beast. Even in that morning twilight, disease was man's ravager, although we may never know its complete role in the disappearance of those peoples that antedated our history.

With the inception of recorded history, man's destiny and disease are so interwoven that it is almost difficult to separate the threads. We are able only to scan some of the highlights, speculating casually upon their implications. Most obvious, of course, in this long record of disease and its influence on human history, are the great scourges that decimated entire peoples, rendering them a prey to their enemies, annihilating them in the slow agony of degeneration.

Until recently, the historian—reluctant to remove man from his role as the wilful master of his fate—failed to give disease its due, in the great historical changes. But it is difficult for the dispassionate student to ignore the ominous presence of pestilence as the threshold of almost every epochal transition. Like an entrepreneur, its macabre devices usher out the old cycle to make way for the new.

It is estimated that in the first seventeen centuries of our Christian era, plague appeared with fatal intermittency on the average of every four and a half years. And while the brevity of this sketch prevents us from venturing too greatly into the annals of pre-Christian history, we know that disease was then, no less a constant peril to life. One has only to study the Rig-Vedas, the Zend-Avesta, the Books of Confucius or the Buddhist Sutras, to realize that the threat of disease brooded over all man's ancient days. In our own Scriptures, plague and disease provide the accompanying organ-note and while the historian and physician may disagree with scriptural utterances as to the causes of the great Egyptian scourges, we know that by the Thirteenth Century B.C. plague had so debilitated Egypt as to permit the Jews to escape from their vassalage.

So, too, in Greece's history. With all truth, we may say that Plague, even more than any alien arms, proved the undoing of Athens. Never partisan in its attentions, disease appeared in Athens at the very time when Sparta was threatening its gates. Learning of the presence within Athens of this adversary, more terrifying than Athenian arms, the Spartan forces turned back. But within Athens, the plague continued its work—the long dissolution of Greece set in. The military was so decimated that the attempts to attack Sparta were lost before they were

begun. Pericles—that light of Greece—himself became a victim of the plague and with his death the Glory that was Greece had past, and the Gotterdaemmerung of Parnassus had set in. But the gods of Parnassus had succumbed not to man, but to an ignoble enemy; the rodents of Asia.

There is an awesome variant of the story six centuries later in Rome. Sparta had come and gone. The passion of Nazareth has passed almost unnoticed. Rome has reached its ultimate magnificence in the Antonines, a period called by Gibbons, “the happiest in the history of mankind.” A happiness, alas, how fleeting! For at the very beginning of the reign of noble Marcus Aurelius, rebellion begins to stir in the Syrian city of Saleucia. The armies, dispatched from Rome to quell the uprising, return, not only with the laurels of victory, but with the seed of Rome’s eventual destruction—the plague. For fifteen years it ravaged Rome. When it had finally spent itself, Marcus Aurelius himself had died, believed its victim. And with his death the Roman panoply fell apart. From his *Meditations* we may well take the moral of our story: “Observe how ephemeral and worthless human things are and what yesterday was a little mucus, tomorrow will be a mummy or ashes. . . . Nature which governs the whole will soon change all things which thou seest and out of their substance will make other things and again other things from the substance of them, in order that the world may be ever new.”

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It would be difficult to set down, in all its intricate detail, the chronology of pestilence in the succeeding Centuries, and its effect on mediaeval history. It struck, with ominous fatality, at times one country, at times another—pagans, Christians; kings, beggars; masters and serfs succumbed to its assaults. In the Fifth Century it stayed the advance of the Hun; in the Sixth it attacked Byzantium, sparing only the Arabs, who were thus able in the name of Allah to penetrate the European stage. It aided the Lombards against Italy and, in the Tenth Century, frustrated the armies of Otto. In the Eleventh, it decimated the German army in Rome, and in the Twelfth defeated the soldiers of Barbarossa. Time after time, it frustrated the efforts of the Crusaders, killing St. Louis himself, and allotting to Christendom, instead of the Holy Sepulchre, the thorny crown of disease and infection.

These are but a very few of Plague's ravages, which time and again transform Europe of the Middle Ages into a charnel house. But, in the light of subsequent history, they appear as steps to a horrendous finale; the planetary conflagration which was the Black Death.

It is doubtful if in all recorded history any force has so changed the course of human destiny as did this pestilence that scourged the world. Over the course of four centuries, it moved relentlessly over the face of the earth, consuming one people after another; decimating cities; depopulating nations; devastating continents. Not even the present war, which alone approaches in its world scope the Black Plague, will have affected so profoundly the course of human existence. When the Black Plague had spent itself, nothing in man's life remained quite the same. As Belloc said, "it was the one approach to a break in the continuity of human history."

Like many of the great plagues, it rose in the East—chroniclers tell us, it began in China, "following a great mist and stench". Thence, along the trade-routes, it passed to India, Persia and Russia, and Emperor John Catacuzene tells us of its presence in Constantinople by 1347. In October of that same year, it appeared in Europe at Messina, where, according to the Franciscan Friar, Michael of Piazza, and others, twelve Genoese galleys had taken refuge from a pursuing enemy. "These Genoese," says our Friar, "bore in their bones so virulent a disease, that anyone who but spoke to them was seized by a fatal illness and in no manner could escape death."

For the next four hundred years, writers in every corner of Europe were setting down additional macabre chapters of the story, tracing the plague's unarrestable advance from Malta, Cyprus, Greece, Sicily, Naples—on to France, Italy and Spain; then moving to Britain, Germany and Russia. Having saturated with infection all the known world, it became endemic in the countries it had ravaged, and flared up again and again until its final European outburst from 1663-68. Thenceforth, it trailed off into Russia, continuing to reappear there for the next hundred years.

The casualties of all wars are dwarfed by the mortality figures of this Plague—estimates of its victims range from Pope Clement's figure of almost forty-nine million to Hecker's estimate of twenty-five million. Suffice it to say, that the web of Europe's population remained completely threadbare—some 200,000 market towns had been wiped out,

in its course. Avignon reported a loss of two-thirds of its people; Venice, of 100,000; Boccaccio declared that Florence lost 100,000 of her 130,000 souls. England's clergy alone were depleted by 25,000. These are but a few of the devastating statistics of the Plague.

The effect on history of such a depletion of human forces is almost difficult of imagining. By wiping out great segments of population it shifted the trends of human activity. For instance, by annihilating a large portion of the mediaeval clergy, those guardians of Middle Age Scholasticism, it left the Church to heirs unprepared to cope with the spiritual unrest of Modern Man as he emerged from his mediaeval sick-bed. Thus was the Reformation precipitated.

By decimating the ranks of feudal lords and serfs it destroyed the manorial system. By thinning out the supply of workers, it tripled the wages of the available supply, and gave impulse to restrictive legislation and class struggles.

It unloosed swarms of lawyers who grew opulent in arguing the cases of succession and inheritance. It bred charlatans and rogues eager to profit by the chaos. It drove agricultural workers into the crowded urban centers and hastened the Industrial Revolution. It set men moving and migrating—within Europe to depopulated cities, whose rulers held out special enticements to immigrants, even be these thieves or criminals. It set men moving away from a Europe infested—bringing the cycle of discovery and colonization to its height, even as Europe's long Dance of Death continued.

It aroused strange libidos which translated themselves into cults such as the flagellants, the chorisants, the Children's Crusades, and a hundred others. All of Europe became a vast Witch's Sabbath, like some fantastic canvas of Hieronymus Bosch. To sum up, the Black Death turned the known world into a seething cauldron out of whose final residue emerged Modern Man.



During the lengthy play of this major holocaust, other diseases were bursting out in lesser violence in various parts of the world, each pressing its own victory. Malaria, smallpox, typhus, leprosy, scurvy, syphilis, dysentery, and many others; each presents a saga in human misery with its subsequent influence on human history. Scurvy, for instance time and again delayed and recharted the course of discovery.

looming as a more dread terror to the early sea-farer than unfathomed seas and legendary monsters.

Malaria, which Osler termed the "greatest destroyer of the human race," seeped the strength of nations through the centuries, transforming vital peoples into weaklings. Typhus, lying in ambush for army after army, rendered military victories meaningless by wiping out victors after they had conquered their foes. Syphilis, said to be the gift of the Spanish Conquistadors to the Motherland, which verily avenged Atahualpa, the Inca, by consuming forever after the armies of all Europe. Yellow fever, that guarded the American tropics more zealously than Yankee doctrines; twice staying France from invading the Hemisphere, once at Haiti and again at Panama. There are many more diseases too numerous to recount.

It is strange indeed, that save for a rare few, historians should have overlooked the historic consequences of all these assaults on humanity. Such classic historians as Thucydides, Lucretius, Herodotus and Plutarch, who lived through their challenge; or a later classicist, such as Niebuhr, sensed their importance. It is less to the historian than the literati, the poet, the cleric, the satirist and the artist that we must look, in studying the long chronicle of disease as a *force majeure* in human history; on rarer occasions to the physician. Fortunately we are able to weave a continuous thread of this story, as we follow the majestic account of a Thucydides, through the chronicles of the Kilkenny Monk, Procopius, Petrarch, Manzoni, Erasmus, down to a Boccaccio, De Foe, a Pepys or a Webster. It is a record of humanity frustrated by an unintelligible force; for as Niebuhr says, "it is not superstitious or even pious to look upon great plagues as a conflict of the terrestrial forces with the development of mankind." Most illuminating it is to study man in this long chronicle; under the threat of danger, the fabric of human relations wears thin; families separate; moral and ethical codes become meaningless. At times, however, this tempering gives renewed strength to man's inner strivings.

As impressive a picture of this story comes to us through the labors of the painters. Titian, for instance, whose paintings of the hero-saints of the Plagues—Roch, Sebastian, Cosmos and Damian—take on the symbol of supplication, as he himself is stricken. Or a Dürer, whose brush dips in the bile of the sufferer, himself. An entire panorama of human agony is rendered through a Simone Martine, Rubens, Guido Reni,

Caracci and many others.

And what, we may ask, of the physician during these times? Betrayed by its proponents and despised by its antagonists, no profession was ever so buffeted about as medicine in these tidal waves of human ailment. A pitiful remnant of medical men remains faithful to their calling—for the rest, as Guy de Chauliac, physician to Pope Clement VI, writes, their record is a mortifying spectacle of the frailty of mankind. On occasion they rise to grandeur, like an Hippocrates, who expends his frail utmost to aid his contemporaries, confessing finally to the possibility of a divine instrumentality in the devastation which he cannot stay. On the other hand, a Galen, physician to Marcus Aurelius, flees Rome at the first danger, returning reluctantly two years later at the exhortation of the Emperor, then writing a history of the plague brazenly plagiarized from Thucydides.

In Genoa, the Senators search the city vainly for three doctors who have remained to aid their fellows—though the black record is eventually erased by such a physician as Marco Leon who voluntarily left the then safety of Perugia, to aid plague-stricken Genoa; or a Chalin di Vinario, who even as he exposes his own life, ironically extols the physicians “who are prudent enough to hold back.” Even the great Sydenham succumbs to the urgings of his family and puts London and the Black Death behind him—while the less-heralded Heinricio Sayer fearlessly attends patients, poor and rich alike, until he himself succumbs.

It is a curious record. But more curious, in the light of present-day medicine, are some of the medical expedients to which the doctors of the day resorted; amulets, bags of arsenic worn near the heart; the chewing of wormwood steeped in lemon; moss from the skull of a man who has met violent death, etc. It is little wonder that a Margaret Paston writes to her husband, in 1414, “For Goddys sake, be war what medesuns ye take of any fisusyans in London. I shall never trust to them because of your fadr and myn onkyl whoys sowlys God assuyle.” So low did the repute of the doctor fall in the opinion of his contemporaries that in St. Lo, in 1601, the physician Marquier was accused of magic because he healed more of the ailing than his colleagues.

Sensing the impotence of the physician, the people themselves sought other panaceas. They turned their hopes most often to the self-abnegating men and women who nursed them, when their closest had fled. It

is these half-legendary figures such as Roch, Gerhard Groot, Sebastian, Cosmos and Damian, Procopius and others, who emerge out of the Middle Ages, with the aureole of hero-saints, anointed by the abysmal misery of an age in which humanity was unevenly pitted against its ancient antagonist—disease.

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And now let us turn from the larger canvas to its detail. Here our pattern is far more intricate and also more controversial—for it will always remain a moot question as to how greatly the life or death of any individual, his frailty or health, can affect the course of history. Tolstoy, for instance, decried vigorously the suggestion that Napoleon's illness at Borodino had turned the tide of battle. For him—as for others who see history as an unarrestable tide, as Schelling's "continuous revelation of the Absolute accomplishing itself"—the individual fades into a limbo of obscurity. For those, however, for whom history is the cumulative labor of generation on generation, man placed in a role of destiny may be important indeed. As Benedetto Croce says, "Let him who cuts individuals out of history but pay close attention that either he has not cut them out at all, as he imagined, or he has cut out with them, history itself."

On this premise—and it must be the premise of this sketch—the indisposition of Napoleon at Borodino becomes significant. Even more, the fact that Napoleon by the time of Borodino was perhaps already doomed by the alleged gastric cancer which was ultimately to kill him at St. Helena. The spasms which, time and again, in these later years, prostrated him, might well have been the real ally of the British and the Holy Alliance; might well, as Voltaire put it, have announced that God was already bored with the Corsican.

Let us go further. As witnesses ourselves to an epoch darkened by evil genius, we may find it profitable to analyze the physical composite of the Napoleonic man, for there are certain analogies that emerge in a scrutiny of these Luciferian figures that dominated their lives. In contrast to their frenzy to conquer the world, we uncover strange timidities, sexual inhibitions and perversions; in short, endocrine imbalance. Napoleon, so passionately anxious for an heir, could father only the unhappy and sickly L'Aiglon. As Anatole France perceived him, he was a buffoon who set the world by the ears, because he was unable to enjoy his own

marital bed. Caesar, imposing his will on the world, philandered with equal promiscuity among men and women. Hitler, withal his frantic *Weltanschauung*, finally will probably only exude the miasma of the homosexual and megalomaniac.

Nor are lesser personages spurned by disease in its manipulation of history—it accompanies princes and royal scions in their marriages of convenience, carrying the mental and physical taints of the dynasties across the chess-board of Europe. Its effective servant—inbreeding—does the rest and accomplishes the pollution of Bourbons, Hohenzollerns, Hapsburghs and Romanoffs. How masterfully, for instance, with one stroke, it demolishes the Romanoffs and Spanish Bourbons, with marriage as the enticement. For what royal princes would not have relished an alliance with the granddaughters of the great Victoria! Yet to both Nicholas of Russia and Alfonso of Spain, their marriages brought the fatal Battenberg bridal gift. The heirs apparent to both houses inherited the hemophilia which is one of the taints of German royalty. Surely, to this fatal blood strain must be attributed the hastened revolutions of both Spain and Russia. And what an episode for the “Garden of Horrors” is this final Russian Grande Guignol of the Mad Monk, the terrorized Tsarina and the little Tsarevitch!

Deftly, also, has disease dissipated other dreams of Empire; Attila suddenly stricken; Alexander conquered by fever; Henry V of France; Charles V, almost attaining the dreamed-of European Empire, merely to be conquered by gout; witness the rapid disintegration of his vast inheritance under fanatical Philip II, with the melancholy strain of his mad grandmother working tumult within him. Gout may also have helped to rob Britain of her greatest colony, when it deprived George III of the counsel of Chatham, the one minister who was sympathetic to America and might have won over the king. Gout and its effect on the affairs of men might alone, in fact, well be the topic of a complete study, as Sydenham (himself a victim) points out.

What a field for study, also, are the numerous royal psychopaths—a veritably inexhaustible field in which the psychiatrist might collaborate with the pathologist and eugenicist. Take Frederick the Great, as a youth beauty-loving, charming, happy-go-lucky; goaded by his father into the brutal and relentless warrior. Impotent by twenty-three, he pursues a loveless life, as famous for his aversion to bathing as for military genius.

Or Henry VIII, who began life as a pleasant, not-too-hopeful second son and was precipitated by the death of his elder brother onto a throne, to become a lecherous, syphilitic and finally paretic king whose physical appetites sow the seeds of Britain's problems for generations. Brooks Adams, philosophizing on history, makes the comment that had Henry been "hampered with scruples, honour, truth or conscience, he too might have been undone". A comment that might well apply to many of Europe's royalty and for much the same reason.

And now, with special appreciation of its bitter fruits for our times, we might mention another historic episode—with Wilhelm Hohenzollern of the withered arm playing the chief role. This deformity (brachial palsy) was a birth-gift for which the late Kaiser never forgave his parents. And yet, pleasant enough parents they were—Frederick III married to the daughter of Victoria and growing ever more sympathetic with the democratic institutions of England. How unlike the ravenous entourage of their Prussian court! Mere weeks after his ascension to the throne, disease, like some apocalyptic rider, overtakes Frederick—in the form of cancer of the larynx. He is desperately anxious to stay alive—for no sovereign ever had fewer illusions about his heir, or the menace that his succession might mean to the peace of the world. From our present perspective, we see an ominous augury in the obscene eagerness with which Wilhelm awaits his father's death, even penning a pompous edict of accession, long before the physicians have even agreed on the fatal character of the disease. Here, alas, disease plays the villain's accomplice. Frederick dies, and, with his passing, generations of the world's youth are doomed to bloody martyrdom.

Or let us examine another episode—this time with the same disease making a graceful withdrawal. In June 1893, President Grover Cleveland discovers that he, too, is stricken with cancer of the superior maxilla. It comes at the most critical moment of his administration. Antagonisms are running high over the "free silver" issue; the President, an ardent opponent of the measure, is prepared to ask for a repeal of the "free silver" clause although his own vice-president is an advocate of the measure. A financial crisis will inevitably be precipitated even by a rumor of his illness. Therefore, at once and with complete secrecy, the President and his physicians arranged an operation on the Yacht Benedict, in Long Island Sound. In two successive operations much of the President's jaw was removed and an artificial or dental moulage

substituted. A month and a half later, Cleveland appeared before Congress, appealing for the repeal of the free silver clause—and won his plea. No one was aware of the crisis through which he had passed—nor is it mentioned in the fifteen subsequent years in which Cleveland lived, free from recurrence of the malignant tumor. Only after his death was the episode disclosed by one of the surgeons who had participated. Here disease is seen in a rarely amenable mood—for once moved, we may hope, by the dignity and merit of the victim, although modern medicine would rightly lay the victory to the quick diagnosis of the disease and the unhesitating attack upon it.

Less felicitous in their outcomes are the numerous sudden deaths which often have altered historical finales; Mirabeau, the one strong force which might have averted the blood baths of the French Revolution; Cavour, at the moment of Italy's great need of him; Baron von Bilbesten, whom Asquith believes should have averted the First World War—perhaps preventable deaths, which may have changed the narrative of history.

These are but a few of the episodes in the phantasmagoria of kings, warriors and statesmen, but they permit a rapid glance at the work of that unpredictable arch-strategist, disease.

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But then history is not alone a tale of kings and warriors. There is more permanent history created by scholars and artists. Here certainly, the historical credos of Schelling and Croce might well merge—for where, if not in the creations of man's mind and spirit, is the Absolute constantly accomplishing and reflecting itself? In this phase of our sketch, concerned with disease and its effect on history through genius, a pattern unfolds in which disease seems most often to work on the side of the angels. Nature, it would seem, as the most thrifty of husbandmen, will not waste a drop of the passion called genius, and uses even pain for its purposes.

As Sigerist points out, disease is an experience, and the artist (let us add also the scientist and philosopher), being the most sensitive of men, can hardly fail to be affected by it. Yet it is not alone in its psychic influence that disease affects genius. Even the pathologic and toxic incursions of disease seem to bear a direct relation to his creation and, very often, to the very type of his creation. We are beginning to dis-

cern, although we cannot always explain, this relationship—and critic, historian and physician should find an excellent field of common labor in studying the patterns together.

Like fire, which heats as it consumes, disease seems to release a creative glow in the wasting body of the creator. Even when it shortens life, as in the case of a Shubert, a Schiller, a Doctor Laennec, or a Mozart, it has so spurred the spirit in its race with death as to have gained the full bounty of creation, within the shortened span.

Tuberculosis, for instance, is so interwoven with man's creation, that it would be impossible to list the innumerable artists and scholars who labored with its consuming breath constantly upon them. And there is no mistaking the character of their work. Dr. John Brown of Edinburgh called tuberculosis "that sad malady in which the body and soul burn together—as in oxygen gas—as if knowing their time is short." A creative intoxication, always speedward, pervades their offerings; Watteau visioning a perpetual Arcady, which he might never enter; the nostalgic ecstasy of a Shelley, a Keats, a Katharine Mansfield, a Lanier, the doomed Brontës, Stevenson, and a host of others.

To see the tuberculous great in best relief, compare a Francis of Assisi, envisioning religion as an eternal ministry to beauty; and Loyola, lamed by his wound, narrowing his faith into a terrible scourge of self-discipline and vigilance. In the Assisian, that "morning star of the Renaissance," we see the epitome of the tuberculous genius, whose spiritual passion rises as the body wastes, leaping to death as it were, with a joyous "Hymn to the Sun." Sometimes, as in the case of an Emerson, a Goethe, a Kant and especially a Spinoza, the spiritual urging of the tuberculous genius becomes so profound as to inspire a universal message on a cosmic key. At other times, when surcease of pain is sought through opiates, as in the case of Poe, Coleridge, Rossetti or Francis Thomson, we can detect a new note in the creative expression, the "stigmata of the drug imagination" as it is termed by Jeanette Marks, who rightly points out that what is often the most beautiful in their works, is the most deranged. A similar distortion of the spiritual focus is alcohol's contribution to the work of a Dowson, a Beardsley, a Joyce or an Andreyev.

The apotheosis of the creative genius, sinking through illness and drugs, to produce its most lofty utterance, is seen in Francis Thomson, who writes "The Hound of Heaven" in the midst of his ultimate phy-

sical humiliation. In his awareness of this strange creative anomaly, he utters an outcry which might well serve as our own query; "Designer Infinite, must thou char the wood ere thou canst limn with it?"

Now let us turn to disease in the role of chastiser—here its rebuke is subtle enough to arouse the determination to compensative creation. Beethoven's deafness was of such character. As he himself wrote, "How am I to admit infirmity in the one sense which should have been more perfect in me than in others?" Yet out of the silence which shut out a strident world—or because of it—Beethoven found the flood of his extraordinary harmonies. Undoubtedly, Milton's blindness served also to evoke the spiritual and philosophical currents which gave voice to "*Samson Agonistes*," "*Paradise Lost*" and "*Paradise Regained*." No less can we omit the deformities of Byron, Hawthorne, Steinmetz, a Pasteur, a Scott, in appraising the character of their creative endeavors.

Syphilis has also played its part in harassing the genius to articulation. Reaching its final stage in Nietzsche, it is responsible for the terrible brilliance of his "*Zarathustra*". And to its incursions may well be laid many of the passionate utterances of a Verlaine, a Beaudelaire, a Heine. At times the genius is aroused to cynical and irascible protest in his work against the prodding of disease—Sam Johnson against his scrofula; Molière against his lifelong need of recourse to doctors, who for him "know the Greek names of all diseases, how to define and classify them, but of curing them know nothing at all." He found some measure of vindictive satisfaction in "*La Malade Imaginaire*" and other of his satires. An entire list of artists, even while they painted the world's great treasures, also suffered the constant encroachments of disease—among them Botticelli, Leonardo, Dürer, Georgione, Van Gogh, El Greco, and many more.

As for insanity and genius, they have so often been fellow-travelers that Lombroso and others mistakenly identified them, one for the other. However, it is rash for those of us "who pass for sane," to pronounce judgment upon the dwellers of a borderland into which we ourselves cannot adventure, and which may finally prove to be a region of larger reality. Is it insanity that dictates Coleridge's "*Kubla Khan*?" At what point does Rousseau, the genius "born dying," who changed the thinking of an epoch, transcend the limits of the rational? And where shall we draw the tenuous line between the seen and unseen which were such verities to a Tasso, a Blake, a Lamb, a Swedenborg, a Joan of Arc, a

Chateaubriand, a Swift, a Doctor Pevsici, and even a Christopher Columbus?

Certainly in this province of man's intellectual and spiritual creations, as they are affected by disease, we reach the most intriguing and challenging phase of our thoughts about disease's influence on man's history. Genius itself remains perhaps the most elusive of human phenomena, and in the few examples we have cited of its relation with disease, we perceive that it can effect its own alchemy. Here is an agent—disease—which works havoc in the thinking and performance of average men; when it is brought into contact with the philosopher's stone called genius, a transmutation is effected. Genius reins even this agent of dissolution for its ends. Here for the first time we see disease, if not conquered, at least foiled or tamed. This metamorphosis of disease from enemy to benefactor should provide a theme of endless fascination and instruction for the student; and the few, perhaps obvious, examples we have cited may provide a point of departure.

Suffice it to say, we here again become aware that the protagonist of our sketch is always among us. Timeless and unwearied he walks through centuries, associates with geniuses and fools; kings and beggar—thus far, with war the only constant in the continually changing pattern of life.

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And now, in closing this cursory study of disease and its influence on man's history and destiny, let us take a final glance at the entire picture. Earlier in this study, in our discussion of plagues and epidemics, we paused at the dawn of the Modern Age. By this, let it not be deduced that we have left plague or epidemic there behind us. Alas, not so! While humanity has learned, since those early centuries, to travel at great speed, it has never been quite fast enough to outdistance Disease. He is always at our shoulder, if not indeed ahead of us.

True, the Black Death has disappeared—but this was not of our own doing. It spent itself; in fact, as an added sop it seems to have carried along with it Europe's leprosy. Since that day we have had our epidemics. Of most recent memory is the great Pandemic of 1918, which revealed modern man as helpless on occasion as mediaeval man. World War I also disclosed that, despite our advances, we still do not entirely know how to by-pass the enemies which waylay our armies. True, our

western fronts in this war were saved by maximum precautions. However, in the Serbian, Russian and other eastern armies, typhus, unimpeded, accomplished its ravages as relentlessly as in Mediaeval wars. From 1918-1922 an estimated twenty to thirty millions of cases of typhus occurred with 10 per cent fatalities. Lenin, as Dr. Sigerist reminds us, regarded this as his first enemy—and remarked that "either socialism would defeat the louse or the louse would defeat socialism." World War II has provided another critical test of our progress with results indicative of surprising improvement.

All this may make modern man pause in his over-confidence. This is not to say that we have not made progress in our struggle against disease, nor that we are without victories to our credit. For one thing, we have learned better to insulate ourselves, through quarantines, sanitary and immigration laws, so as to lessen the danger of epidemic. For another thing, we have discovered new prophylaxes and cures against some of the most persistent of our diseases.

We have learned and begun to practice what the Middle Ages overlooked; that sanitation or the lack of it and subnormal standards of life have a direct influence on the spread of disease. We now understand that disease is no metaphysical matter—it is connected with man's way of life. This is the lesson which even royalty of our earlier centuries never wanted to learn. Thus, the courts of Louis XIV or Elizabeth—at this distance—seem dazzling in luxury and grandeur. However, modern man venturing into them would not find them to his olfactory or visual liking, we are sure. Fragonard, Watteau and Gainsborough charitably omitted from their paintings numerous realistic details. This enhances their beauty but eliminates them as documentary evidence for our purposes. More truthful are the words of a Ben Johnson as he reproaches the pock-marks which were almost universal; "Could there not be one beauty in an age and free from thee?" Closer to truth, also, is Mme. de Montespan's farewell shaft at Louis XIV, indelicate but frank, which gives us light on his personal habits. Modern man, at least, has learned pleasanter ways of living—and thereby has exposed himself less to the diseases of filth.

Perhaps the greatest victory over disease has been in the extension of man's life expectancy. In the Fifteenth Century, the child could have expected to live from twenty to twenty-five years; today we have extended his hope to sixty. As Peyton Rous says, however, we have

saved man from the diseases of childhood. We still have not removed him from attacks of cancer, high blood pressure, heart ailments and other diseases of middle age. However, it is a signal victory, to have eliminated much of the waste of human forces which comes from early death. Thus the potential leader, genius, or even artisan, may contribute his full life's labors to the sum total of man's necessities.

One of the most significant advances is in the practices of the medical profession itself. As we scrutinize our present medical world, in contrast to its mediaeval counterpart, we take reasonable satisfaction in new professional attitudes. It is to be expected that medicine will never again have recourse to the expedients to which it once, not too long ago, resorted; amulets, incantations and the strange witch's brews, which passed for respectable *Materia Medica*. Doctors today evidence a greater humanity than their predecessors who virtually flayed their patients into cure or death. Early chronicles indicate that frequently the speedy death in an auto-da-fe was preferable to the solicitudes to which Middle Age doctors subjected their patients. The horrible inquisition to which even royalty was subjected in its fight against death is evidenced in an illuminating account, quoted by Haggard, of Charles II's bitter final hours. Having fallen into a convulsion, due it is believed, to an embolism, the king was put through a series of bleedings, blisters, emetics, purgatives, plasterings, combined with so repugnant a succession of medicines, including drops of human skull, as would have killed a well man, and did certainly accomplish for Charles what the embolism began, but with added discomfort. As a Seventeenth Century physician, John Ward, writes in his diary, "It may be said of some physicians that they cure their patient, as Nero did his senators, by cutting their veins, or rather their throats."

True, these victories do not seem too many. Nevertheless, they indicate progress. Even more, they give hope. For within the accelerated speed of the past century, medicine has covered greater ground than in the forty centuries which preceded it. On this advance, medical leaders base their belief that humanity may yet reach that Elysium in which disease will no longer prey on mankind.

For the present, however, Disease still stands relentlessly barring our way. We shall have to wrestle with him often and fiercely before the final conquest. Hence for today victory must lie in the struggle itself. And there is indeed signal inspiration in the fact that men today,

more than ever, are expanding selfless days and nights in unquiet and determined search, to release their fellows from this ravager. Like the true man of Carlyle, for whom self-abnegation and perpetual labor are allurements, these scientists are narrowing the province of disease's insatiable predations. By illuminating the great mystery of the human complex, they are arming man with self-knowledge—the surest weapon to cope with his ubiquitous enemy. Thus they are gradually giving design to life and a purposefulness to history. But modern man, no less than his progenitors, still faces the age-old challenge; the conquest of war and disease. They are still the supreme tests, still the witnesses to his failure thus far. On his eventual ability to conquer them lies his vindication. Is he forever to remain only the helpless instrument of forces which constantly buffet him about? Or is he to emerge at last, in possession of his full powers, the wilful master of his destiny?

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SECTION ON MICROBIOLOGY

MAY 19, 1948

I. EXECUTIVE SESSION

- a. Reading of the Minutes
- b. Election of Section Officers
For Chairman—Gregory Schwartzman
For Secretary—Harry Most
- c. Election of five members of the Advisory Board
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Colin M. MacLeod (1948-50)
John G. Kidd (1948-51)
Rene J. Dubos (1948-52)
Ralph S. Muckenfuss (1948-53)

II. PAPERS OF THE EVENING

- a. Studies on the mechanism of polysaccharide inhibition of virus multiplication
Harold S. Ginsberg (by invitation) and Frank L. Horsfall, Jr.
Hospital of the Rockefeller Institute
- b. Stability of bacterial viruses in solutions of salts
Mark H. Adams, Ph.D. (by invitation)
New York University College of Medicine
- c. Dextran-forming streptococci from the blood in subacute endocarditis and from the throats of healthy persons
Edward J. Heire (by invitation)
Cornell University Medical College
- d. Effect of nucleic acids and carbohydrates on the formation of streptolysin
Alan W. Bernheimer, Ph.D. (by invitation)
New York University College of Medicine
- e. Treatment of amebic hepatitis with chloroquine
Neal J. Conan (by invitation)
New York University College of Medicine

Studies on the Mechanism of Polysaccharide Inhibition of Virus Multiplication

HAROLD S. GINSBERG (by invitation) and FRANK L. HORSFALL, JR.

From the Hospital of The Rockefeller Institute for Medical Research

It was demonstrated recently^{1,2,3} that type specific capsular polysaccharides of Friedländer bacilli alter the course of infection with PVM and mumps virus. Multiplication is inhibited when polysaccharide is injected as long as 4 days after inoculation of either virus in appropriate hosts. Polysaccharide does not inactivate or demonstrably alter the virus, nor is a virus-polysaccharide combination formed. Present evidence indicates that polysaccharide does not act as virus "receptors" of host cells and even in the presence of large quantities of

carbohydrate virus is adsorbed by host tissue thereby completing the first step in infection.

The capsular polysaccharide of Friedländer bacillus type B (Fr. B) does not inhibit multiplication of influenza A, influenza B and Newcastle disease viruses² which multiply rapidly. This suggested that the latter viruses may require different metabolic systems within the susceptible cells of appropriate hosts than do mumps virus and PVM which increase in concentration at a slower rate.

The viruses of influenza A, influenza B and Newcastle disease interfere with the multiplication of each other.^{4, 5, 6} If these viruses did require host metabolic systems different than mumps virus and PVM for multiplication, it seemed possible that the former viruses would not interfere with the multiplication of the latter. Experiments were carried out to test this hypothesis.

Varying quantities of mumps virus were inoculated into the allantoic sac of chick embryos, and followed in 4 days by inoculation of varying quantities of the PR8 strain of influenza A or the Lee strain of influenza B virus. After a further period of 2 days, the allantoic fluids were removed, and their hemagglutination titers determined in the presence of a constant quantity of immune rabbit serum, either anti-mumps, anti-PR8 or anti-Lee. When quantities of influenza virus were employed, which were equal to or smaller than the quantity of mumps virus inoculated, both viruses multiplied simultaneously in the allantoic sac.

Due to the fact that the influenza virus strains employed kill chick embryos 3 to 4 days after inoculation, it was necessary to shorten the total period of incubation in order to use these influenza viruses as the first inoculum. Under these conditions, when as much as 10⁶ E.I.D. of each virus was employed, simultaneous multiplication of influenza and mumps viruses was demonstrated.

Influenza A and B viruses mutually interfere in the mouse lung.⁴ If the theory proposed above were correct, then PVM and influenza viruses should not interfere with the multiplication of each other in the mouse. The intranasal inoculation of PVM was followed in 4 days by the intranasal inoculation of a similar quantity of PR8 or Lee virus. After a further interval of 2 days the mouse lungs were removed, and appropriate procedures carried out to determine the presence of PVM and influenza viruses by the hemagglutination technique. In each instance there was simultaneous multiplication in the mouse lung of influenza viruses and PVM. In order to carry out experiments in reverse order, strains of influenza A and B viruses which had not been

"adapted" to the mouse were employed.⁷ When either the FM1 strain of influenza A virus or the B1103 strain of influenza B virus preceded the intranasal inoculation of PVM by 2 days, it also was found that influenza viruses did not interfere with the multiplication of PVM.

Due to the lack of a common host it was not possible to determine whether PVM and mumps virus mutually interfere, as theoretically they should. Present evidence suggests that mumps virus and PVM require different host metabolic systems for multiplication than the viruses of influenza A, influenza B, and Newcastle disease. This may afford an explanation for the fact that Fr. B inhibits the multiplication of mumps virus and PVM, but fails to alter the course of infection with the influenza-Newcastle group of viruses.

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Dextran-Forming Streptococci from the Blood in Subacute Endocarditis and from the Throats of Healthy Persons*

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Through the action of various bacteria or of cell-free enzymes derived from them, sucrose can be converted into *dextrans* (glucose polymers), or *levans* (fructose polymers). Most streptococci do not synthesize either one of these polymers, but some non-hemolytic streptococci do form dextran, others levan, and still others mixtures of dextran and levan. Cultures of streptococci that form one or both of these polysaccharides are likely to become slimy or viscous if sufficient sucrose is contained in the medium. However, "slime from sucrose" (i.e., a slimy or viscous appearance of sucrose cultures) is a wholly inadequate criterion for the presence either of dextran or of levan. Dextrans and levans are serologically reactive polysaccharides; and the application of serological tests in combination with certain chemical and physical tests furnishes a method which is adequate not only for the exact recognition of small amounts of dextrans or levans but also for the distinction of one from the other.

By use of that method, we established the occurrence, in about 40 per cent of patients with subacute endocarditis, of a variety of streptococci that produces abundant dextran (but little or no levan) from sucrose. Important from the standpoint of the pathogenesis of subacute endocarditis is the question of whether or not this newly recognized variety occurs in the throats of healthy people. With Dr. Dorothy Genghof, we examined cultures of bacteria isolated from the throats of 18 healthy young adults with no history of recent respiratory illness. Material from the pharynx was streaked on plates of fresh beef infusion agar enriched with horse blood, yeast extract and glucose; the plates were incubated for 2 days at 37° C either aerobically or, more frequently, in

an anaerobic jar; from 50 to 70 isolates per person were obtained and tested for capacity to synthesize dextran or levan by the previous method.¹

Of the 1096 cultures tested, 296 formed levan, either alone or in mixture with dextran; 20 representative strains of these bacteria had taxonomic features typical of *Streptococcus salivarius*. Twenty-eight strains, obtained from the throats of 9 of the 18 subjects, produced abundant dextran but little or no levan. The supernatant fluids of sucrose broth cultures of those strains showed turbidity on treatment with 1.2 volumes of alcohol, and precipitation in dilutions from 1:100 to 1:10,000 w. v. a dextran-reactive type 2 pneumococcal antiserum, whereas the fluids of glucose broth cultures of the same strains gave negative results; the absence of levan was shown by the failure of the sucrose broth culture fluids to give serological precipitation in dilution from 1:10 to 1:1000 with a potent levan-reactive antiserum, or to show any detectable amount of chemically determined polyfructoside.

The 28 dextran-formers isolated from throats had taxonomic features like those previously described for the dextran-forming streptococci from endocarditis.¹ Their colonies on 5 per cent sucrose agar were small when incubated aerobically; they had the capacity to oxidize hemoglobin and, usually, to produce ammonia from arginine and acid from inulin; and they failed to produce acid from xylose or starch. Twenty of the strains were identical in those properties. These taxonomic features are similar to the description for *Streptococcus s.b.e.*, which Loewe, Plummer, Niven and Sherman² isolated from the blood of endocarditis patients. These authors did not recognize

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the immunochemical feature of dextran formation in their original paper² that appeared simultaneously with our publication,¹ but they later reported³ that sucrose broth cultures of most strains of *Streptococcus s.b.e.* have a viscous or slimy appearance. The same authors, however, maintain^{2, 3} that *Streptococcus s.b.c.* is absent from the normal human throat.

Our dextran-forming streptococci seem to constitute a group closely similar to the *Streptococcus s.b.e.* However, since their exact relationship has not been determined, it seems desirable to apply the tentative term *Streptococcus DS* to our group of strains because the production of dextran from sucrose was used as the primary criterion for setting up the group. As shown in this paper, although present apparently in much smaller numbers than *Streptococcus salivarius*, streptococci of the *DS* variety do

occur in the throats of healthy persons and, hence, may be regarded as a part of the normal flora of the human throat as well as one of the important agents of subacute bacterial endocarditis.

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* * *

Stability of Viruses in Solutions of Salts

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A series of seven coli-dysentery phages were tested for their relative stabilities in broth and in 0.1 N sodium chloride. In all cases the viruses were much more stable in broth than in saline, the most marked difference being with phage T5. This phage is inactivated in accordance with the kinetics of a first order reaction, the half life in saline at 37°C being less than a minute. In broth the phage must be heated to 70°C before the velocity of inactivation reaches this magnitude.

The stability of phage T5 in saline could be increased by adding various divalent cations at 10⁻³ M concentration. Of these, barium, strontium, calcium, magnesium, manganese, cobalt, nickel, zinc, cadmium and copper all had a marked protective effect, while lead and mercuric ions did not protect the phage. The protective effect of magnesium ion against inactivation of phage T5 in saline was titrated over a consider-

able range of concentrations and temperatures. At 10⁻⁵ M magnesium ion the protective effect was barely detectable but at 6 x 10⁻² M magnesium ion the phage was as stable as in broth and further increase in magnesium ion concentration did not further increase phage stability. The first order velocity constants of inactivation at constant temperature varied with the second power of the magnesium ion concentration.

Similarly increasing the sodium ion concentration from 0.1 N to 1.0 N resulted in a tremendous increase in phage stability, the first order velocity constants increasing with the eighth power of the sodium ion concentration.

Ammonium ion also had a protective effect against the inactivation of phage T5 in saline. Various anions tested such as chloride, sulfate and phosphate had no effect either protective or destructive on the in-

feetivity of phage T5. Citrate and oxalate ions accelerated the rate of inactivation of phage T5 to an extent which could be explained on the basis of complex formation with traces of divalent metals. The citrate complexes of calcium and magnesium for instance did not protect phage T5 from in-

activation as did the metallic ions alone.

The simplest explanation of these results would seem to be that phage T5 can form complexes with a number of cations, and that the infectivity of these complexes is much more stable than that of the free virus.

* * *

The Treatment of Amebic Hepatitis with Chloroquine

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The wartime antimalarial drug research program disclosed a number of highly active 4-aminoquinoline compounds of high activity. It seemed logical to determine whether their antiplasmodial activity extended to other pathogenic protozoa. Because more pharmacological information was available concerning chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, it was decided to test this drug against *Endameba histolytica*, an infection prevalent in the New York area. Since this drug is localized within the livers of various animals, and presumably man, to some 500 times its plasma concentration, and since only about 8 per cent of the oral dose appears in the feces, it appeared a priori that amebic infection of the liver rather than of the colon would be the test object of choice.

Preliminary results published previously indicated: 1) That chloroquine possesses in vitro activity comparable to that of emetine and superior to that of Anayodina and Carbarsone, 2) That it is more effective in amebic hepatitis than amebic colitis, and 3) that in daily doses of 0.3 gm of the base for two or three weeks no significant drug toxicity occurred.

To date, chloroquine has produced symptomatic and parasitological cure of 16 out of 31 cases of amebic colitis, and a prompt clearing of signs, symptoms and abnormal liver function tests in twelve cases of amebic hepatitis. This report presents de-

tailed observations concerning six of these cases, four of which were studied at the Presbyterian Hospital, one at the Bronx Veterans Administration Hospital, and the other at the Hospital for Tropical Diseases, London, the data of this case being supplied through the courtesy of Drs. F. Murgatroyd and N. H. Fairley. The other 6 cases were studied by Dr. Howard B. Shookhoff of the Tropical Disease Diagnostic Service at the Columbia-Presbyterian Medical Center.

In the 6 cases reported here, 6 had enlargement and tenderness of the liver, 5 had fever of significant degree (102°F. or higher), *Endameba histolytica* was demonstrated in the feces of 5 and in pus draining from a liver abscess in one, four had involvement of the right diaphragm as manifested by splinting and pleural effusion. There was abnormal retention of Bromsulfthalein in the four cases in which this test was performed, and elevation of the serum alkaline phosphatase in two of five cases in which it was measured. The cephalin-cholesterol flocculation test was negative in the 5 cases in which it was performed.

Under treatment with chloroquine there occurred in each instance within two to four days definite improvement in all the aspects of the clinical and laboratory pattern. All patients regained their previous health and have maintained it over periods of from 2 to 15 months since discontinuation of therapy.

In two instances a comparison has been

afforded between chloroquine and emetine. In one case emetine produced a favorable but incomplete response inasmuch as one month after there remained low grade fever, enlargement and tenderness of the liver as well as anorexia, nausea and failure to gain weight, within a week of treatment with chloroquine all of these manifestations disappeared. The other is the case of Drs. Murgatroyd and Fairley in which there was a draining liver abscess in the pus of which Endameba histolytica were demonstrated throughout various treatment regimes including emetine parenterally, orally and locally by irrigation. The amebae disappeared from the liver pus on the fifth day

of chloroquine treatment and the wound was healed by the twelfth day.

Chloroquine would thus appear to be a safe and effective substitute for emetine in the treatment of extraintestinal amebiasis. Its lack of serious toxic potentialities render it preferable to emetine. When coupled with a superior intestinal antiamoebic drug it should permit complete therapy of any amoebic infection on even an ambulatory basis if the condition of the patient warrants it.

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* * *

Effect of Nucleic Acids and Carbohydrates on the Formation of Streptolysin S.

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Yeast nucleic acid stimulates the formation of a potent hemolysin in cultures of *Streptococcus pyogenes* (Okamoto, H., Jap. J. Med. Sci., IV. Pharmacol., 1939, 12, 167). The properties of the hemolysin indicate that it is probably identical with streptolysin S. It has been found that little or no streptolysin S is formed in chemically defined-medium cultures unless the medium is supplemented with two other factors. Neither one of these factors is needed for growth but both are required for streptolysin S formation. The chemical nature of each has been elucidated and pertinent information concerning them follows:

The first factor is supplied by ribonucleic acid from yeast, wheat, mammalian liver, or streptococci, but apparently not by ribonucleic acid from tobacco mosaic virus nor by desoxyribonucleic acid prepared from several sources, nor by purine- and pyrimidine-mononucleotides or their hydrolysis products. Fractionation of yeast nucleic acid, following enzymatic splitting, has

yielded a polynucleotide whose streptolysin-inducing activity is approximately 100 times that of yeast nucleic acid. The polynucleotide has been partially characterized but knowledge of its exact composition is incomplete.

The other factor is present in peptone and in muscle. It can be replaced by minute amounts of maltose or by somewhat larger amounts of glucosamine or trehalose. As little maltose as M/64,000 is sufficient to cause a significant degree of streptolysin formation. Glucose as well as many other mono-, di- and polysaccharides, are either inactive or active only in relatively high concentrations.

When appropriate concentration of polynucleotide, maltose, and glucose are used, streptolysin S can be produced in a medium the chemical composition of which is essentially defined. Using this information, a satisfactory method of producing streptolysin S in mass cultures has been developed.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHROD, *Editor*

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THE CLINICAL USE
OF RADIOACTIVE IODINE*

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and CHARLOTTE SCHMIDT, B.A.

IT is well known that the thyroid gland takes up iodine.¹ When radioactive isotopes of iodine became available, it appeared reasonable to use this localization for delivery of an internal radiation therapy to the hyperactive gland. As the radioactive atoms disintegrate within the thyroid, they emit beta and gamma rays, producing the same kind of tissue reaction as x-rays, but the irradiation is largely confined to the gland itself.

Two isotopes of iodine are suitable for attempting this type of therapy, I^{130} , with a half life of 12.6 hours, and I^{131} , half life 8 days. The latter was not readily produced until recently, but the former became available in a few localities about 1943, and two groups in Boston employed it for therapeutic purposes in toxic goiter.^{2,3} The results of work started about the same time in other clinics have not been reported.

Since the release of isotopes from the atomic energy pile at Oak

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Ridge, Tenn., it has been possible for suitably equipped institutions to obtain I¹³¹. Accordingly an appraisal of the treatment of toxic goiter with this agent has been undertaken in several hospitals. The study here reported was begun in October 1946; the material is presented as a preliminary report.

PROCEDURE

At the start of the work no adequate basis for dosage planning was available. Decision as to the amount of material to be administered involved taking into account the degree of uptake of the radioactive material by the thyroid gland, and its subsequent release therefrom, as well as of the amount of energy released by the radioactive atoms. Calculations were made as follows: According to theoretical considerations, if a relatively small organ has a uniform concentration of 1 microcurie of I¹³¹ per gram, and the isotope remains there for total decay, the tissue will receive a radiation dose of about 160 equivalent roentgens.*⁴ In the case of the toxic thyroid gland, the iodine gradually leaves the organ at such a rate that the effective dose is reduced to about 120 e.r.

Cases successfully treated with I¹³¹ in the earlier series mentioned above^{2,3} appear to have received about 2000-4000 e.r. When radiation is delivered more slowly, as with the 8-day isotope, a larger total number of roentgens is necessary to produce the same therapeutic result; accordingly in the present series a dose of 3000-5000 e.r. was made the objective. Assuming a 60-gram thyroid, an uptake of 50 per cent of the administered material, and a gradual loss by elimination from the gland, a dose of about 4 millicuries would be required to deliver this radiation. Treatments were therefore started with this as the amount administered to all cases, although, because of differences in gland size and in iodine uptake, there would be considerable variation in the actual irradiation administered. Thus, an appraisal of clinical response to various doses would be made. This was desirable, since it was not certain whether the calculated dose of radiation was optimal, or whether it should be more or less.

Radioactive iodine was obtained from the atomic energy pile at Oak Ridge, Tenn. After proper standardization and dilution, the material was given by mouth, in water solution, the iodine being carrier-

* The roentgen is the unit for x-rays and gamma rays; it is not at present defined for beta rays. Dosage for these latter is expressed in equivalent roentgens; the ionization produced in air by an equivalent roentgen is the same as that produced by one roentgen of gamma rays, when both are properly measured. The unit is abbreviated e.r.

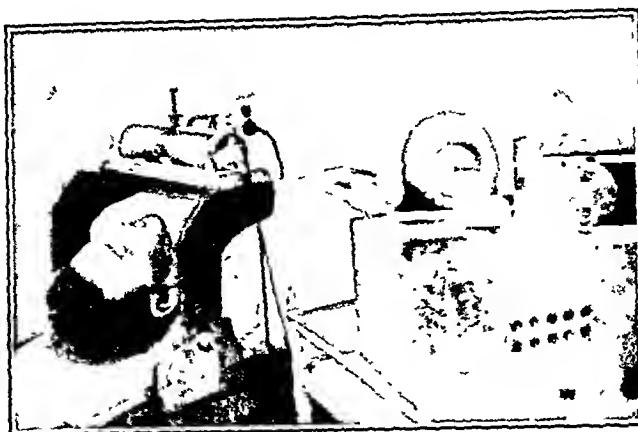


Fig. 1. Patient being measured for radioactive iodine uptake with Geiger counter.

free (i.e., all radioactive). Thus the 4 mc. therapeutic dose contained only about 0.03 micrograms of iodine, which is well below the normal daily intake of the element. In the early cases a tracer dose was not always given in advance of therapy; later this became routine, in order to obtain information about the uptake.

In addition to the therapeutic administration of the material, numerous tracer studies have been made, to determine radioiodine uptake by individuals with normal and diseased thyroid glands. Tracer doses were usually of the order of 50-75 microcuries; the radiation effect on the gland from this amount is considered insignificant.

In both therapy and tracer patients the radioiodine uptake by the gland was measured at different times after ingestion. The patient was placed on a frame as shown in Figure 1, so that the skin over the isthmus of the thyroid was always at 15 cm. distance from the Geiger counter. The first patients were studied from the instant of administration; uptake was followed minute by minute for the first hour, then at 3, 6, 24 and 48 hours. All cases were measured at 24 hours after therapy and weekly thereafter as long as practicable.

Most of the iodine which is not concentrated in the thyroid gland is excreted in the urine, within the first 24 hours. Accordingly urinary iodine output was followed for 24 or 48 hours whenever possible.

The size of the gland was estimated immediately prior to treatment. To aid in this, a series of plasticine models was constructed and their

TABLE I

TABLE SHOWING UPTAKE OF RADIOIODINE BY THYROID GLAND AND URINARY EXCRETION OF THE ISOTOPE IN TRACER STUDIES

Type of Case	Per Cent in Gland at 24 Hours			Per Cent Excreted in 24 Hours			Number of Cases
	Max.	Min.	Aver.	Max.	Min.	Aver.	
A. Patients without known Thyroid Disorder	36	11	21	76	28	52	20
B. Patients with known Thyroid Disorder							
1. Toxic Goiter							
a. Diffuse	76	44	65	27	6	17	28
b. Nodular	67	33	52		10		7
c. Hyperophthalmic	60	54	58	25	18	22	4
2. Non-toxic Nodular Goiter	24	15	19			data incomplete	3
3. Hypothyroidism	4	1	3	62	48	55	5

Tracer doses were 40 to 100 μ c of I^{131} administered by mouth in the form of soluble iodide, carrier free. Uptake measurements *in vivo*, Geiger counter 15 cm. from skin over thyroid.

volumes determined by liquid displacement. They were, for the normal gland, 25 cc., and for the four stages of enlargement, 35, 50, 70 and 100 cc. By palpation it was possible to assign a particular patient's gland to one of these groups, or to a value halfway between two. It is realized that this method is inaccurate, but an approximate knowledge of gland size is essential in evaluating this type of therapy. This lack of accuracy must be kept in mind in connection with any statement regarding dosage.

Radiation dosage was calculated for all treatments according to a formula taking account of millicuries administered, percentage uptake, rate of elimination from the gland, and gland size.⁵

RADIOACTIVE IODINE TRACER STUDIES

The tracer studies were made on normal, hypo- and hyperthyroid individuals as summarized in Table I. The uptake at 24 hours in the normals varied within the relatively narrow range of 15-30 per cent of

the administered amount. In toxic goiter it was over 40 per cent, and in hypothyroidism under 10 per cent. The border regions of 10-15 and 30-40 per cent appear indeterminate. Administration of stable iodine or of anti-thyroid drugs within two weeks prior to the test may vitiate the results.

Urinary excretion in the first 24 hours after radioiodine administration varied from 40 to 70 per cent in the normals and from 10 to 40 per cent in the hyperthyroid cases. The toxic group excreted more of the material in the first 6 hours than in the following 18, probably due to increased renal clearance. In the normals, considerably less appeared in the urine in the first 6 hours than in the remaining 18. Thus the measurement of urinary excretion gives an indication of toxicity, though not as reliable as measurement of gland uptake.

THERAPEUTIC STUDIES

a) *Type case.* Up to the present time 40 cases of unquestioned toxic goiter, given 47 treatments with I^{131} , have been followed long enough to permit some evaluation of the results of therapy. The follow-up period has ranged from 4 months to more than a year. Fourteen of the patients were men, 26 women. Ages ranged from 23 to 57. Eighteen of the cases were primary toxic goiter not treated previously by any means, whereas 22 were recurrent after operation and had received antithyroid drug therapy for some time without satisfactory relief. All but one case had toxic diffuse goiter; no true hyperophthalmic goiter was treated.

b) *Dosage and Clinical Response.* 1. Millicuries. All cases in this series received from 3 to 4 mc. In the 40 patients treated, there were 13 failures after a single dose of I^{131} and 4 more failures in 7 of these patients given second treatments. Thus 34 of the 40 patients were treated once, and if necessary twice, and have been followed for 4 months or more after therapy. Thirty of these 34 have been put into remission, a case success rate of 88 per cent. The other 6 instances of failure with the first treatment have been retreated too recently to include in this report. On the basis of number of treatments given, there have been 17 failures in 47 treatments, or a treatment success rate of 64 per cent. Four instances of transient hypothyroidism occurred following radioiodine therapy, but these returned to normal within a short time.

2. Microcuries per gram of estimated gland weight. With a rela-

TABLE II

TABLE SHOWING RELATION OF SUCCESS OR FAILURE WITH I^{131} TREATMENT AND DOSE IN MICROCURIES OF I^{131} ADMINISTERED PER GRAM OF ESTIMATED GLAND WEIGHT

<i>uc Adm per gram</i>	<i>Number of Treatments*</i>		
	<i>Success</i>	<i>Failure</i>	<i>Total</i>
250	1	0	1
200-250	2	0	2
150-199	9	0	9
100-149	7	2	9
50-99	12	8	20
50	3**	6	9

* Data not available in 3 instances

** These were all second treatments after failure to respond satisfactorily to the first treatment.

tively constant amount of radioactive material, it is obvious that the larger glands collect much less radioiodine per gram of tissue, and hence receive less actual radiation than the smaller. Therefore, as stated above, estimate of gland size is essential, even though admittedly not accurate, to permit calculation of radiation dosage. The number of microcuries administered per estimated gram of gland tissue is related to the result of treatment as shown in Table II. With doses of 100 or more uc per gram, only 2 of 15 cases failed to respond satisfactorily. With lower doses the successes and failures were equally divided.

The actual irradiation of the gland is the result not simply of the uc administered per gram of tissue, but of the uc retained there. There were no failures in those instances in which more than 75 uc were retained per gram. On the other hand, only one case responded satisfactorily to an initial dose of less than 25 retained uc per gram.

3. *Equivalent Roentgens.* The actual radiation dose in terms of equivalent roentgens depends not only on the uptake by the gland, but also on the subsequent rate of elimination therefrom. Dosages calculated according to the formula allowing for these factors are given in Figure 2, with the corresponding results. There were only 2 failures in 13 treatments of 6000 e.r. or more. In the 3000-6000 e.r. range successes

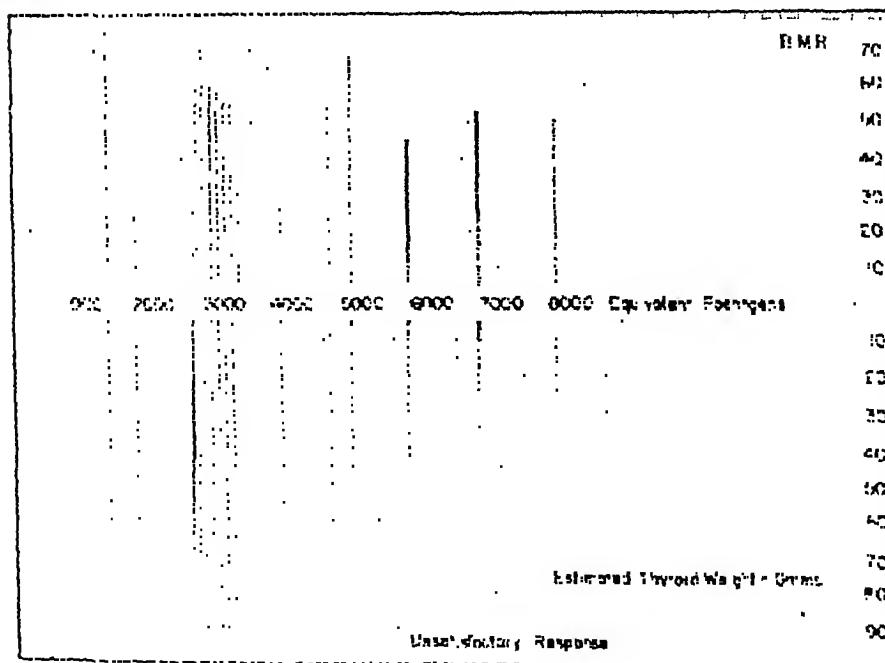
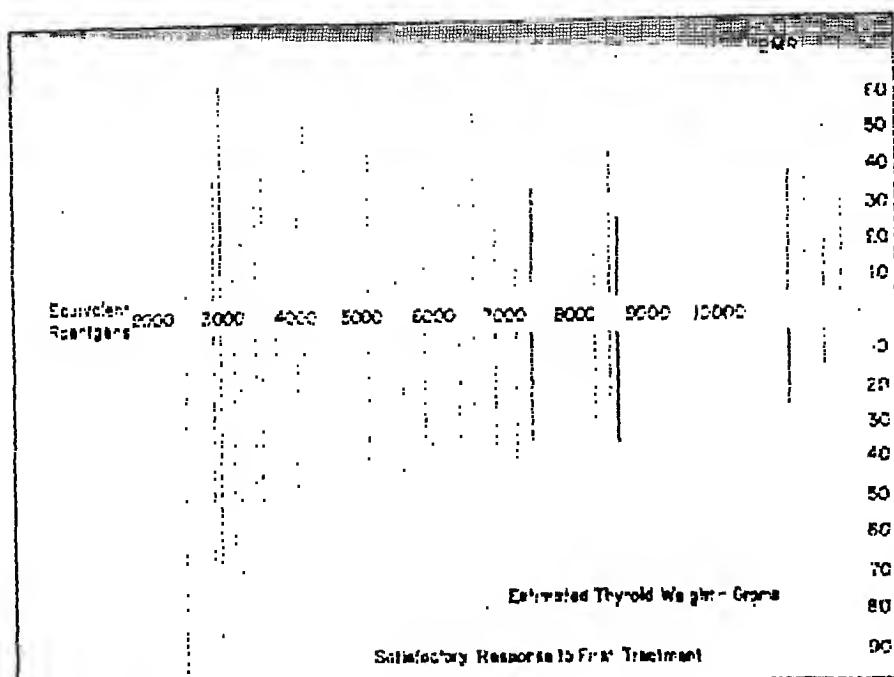


Fig. 2. Chart showing radiation dosage, BMR, and gland size for each individual case. Upper part—successful treatment; lower, unsuccessful. Each patient is represented by two lines, starting at the administered dose of equivalent roentgens. The line extending upward indicates the BMR, the one extending downward, the estimated thyroid weight.

TABLE III

TABLE SHOWING TIME ELAPSING AFTER RADIOIODINE THERAPY BEFORE RETURN OF BASAL METABOLIC RATE TO NORMAL

<i>Months Between Treatment and Establishment of Normal BMR</i>	<i>Number of Cases*</i>
0-1	2
1-2	12
2-3	10
3-4	5

* Data not available in 1 instance.

and failures were equally distributed. The three successes in the lowest dosage range were repeat treatments after inadequate initial responses. The four instances of transient hypothyroidism mentioned above occurred with doses of 2900, 6900, 7400, and 8600 e.r.

c) *Further Analysis of Failure of Treatment.* The factors influencing radiation dosage, as has been stated, are the amount of radioactive material administered, the weight of the thyroid gland, the percentage retained in the gland and the rate of its release. The pre-treatment level of the basal metabolic rate may also be significant. In an attempt to visualize the importance of some of these factors, Figure 2 is presented, to show, for each individual case the gland size, pre-treatment BMR, and dose in equivalent roentgens. This dose takes account of uptake and elimination. The upper half of the figure deals with the successful treatments, the lower with the failures.

As would be expected, most of the failures are in the low dosage region, in which are the large glands. The reason for failure in the three or four cases receiving apparently adequate doses is not clear. Possibly the glands were larger than estimated, which would mean that the radiation doses were smaller than indicated. It may be noted that on the whole the failures show higher basal metabolic rates than the successes.

It is interesting to observe that there are a number of successes in the lower dosage region, which, in this series, means large glands. On the average these successful cases have lower BMR's but this is not always the case. There is apparently an actual region of overlap in dosage

for successful and unsuccessful therapy. It is important to increase the series and to treat large glands with radiation doses of the same magnitude as those received by the smaller ones.

d) *Time Necessary for BMR to Return to Normal.* Although a few successfully treated cases experienced a return in basal metabolic rate to normal in less than 2 months, most of the cases were not in remission until the end of the second or middle of the third month. A few required even longer (Table III).

e) *Complications.* The incidence of complications resulting from radioiodine therapy is not high.

1. Hypothyroidism. Four instances of transient hypothyroidism occurred with I^{131} doses of 3 to 4 mc.; these patients received radiation doses of 2900, 6900, 7400, and 8600 e.r. The symptoms and signs of hypothyroidism were noted in the third to fourth month after treatment, and cleared within the space of a month, with one exception, which required somewhat longer.

2. Sore throat and cough. A persistent sensation of a head cold or sore throat occurred in 6 instances with a hacking cough, and in one other, cough alone, without adequate evidence of an upper respiratory infection to account for it. This appeared several weeks after treatment and subsided about a month later.

3. Tender gland. Marked tenderness of the thyroid gland to palpation was noted in 2 cases, subsiding after several months. The glands became indurated; this characteristic was noted in many cases without associated tenderness.

4. Flare-up of toxicity. Three instances of increased toxicity in the month following therapy were noted. This brought the basal to about 15 per cent higher than before therapy, and was sufficient to create alarm concerning the patient's status, though fortunately neither cardiac failure nor thyroid storm was precipitated in any instance.

5. Radiation sickness. No instance of this complication was noted.

6. Intercurrent pregnancy. Two patients were unwittingly treated in the first 2 months of pregnancy. No apparent harm to patient or fetus has been evident.

f) *Reduction in Gland Size.* In most cases the glands were reduced to within normal limits or less by 3 months following therapy, when remission was obtained. In the instances of failure of therapy, gland size was somewhat reduced, although not to normal limits.

g) *Radiation Hazards.* Two aspects of radiation hazards must be considered, the danger to the patient and to other individuals.

1. Danger to the patient. This might be either immediate or late. The analysis of complications just made indicates that there is no immediate danger to the patient from the effects of radiation. The possibility of late radiation damage leading to malignant change cannot be ignored. However, a calculation of radiation dosage administered to many individuals in intensive x-ray therapy of the neck, and comparison with the doses in this series, indicate that the hazard is not great.

h) *Later Malignancy.* A concensus of opinion based on experience with x-ray treatment of toxic goiter indicates that later malignant complications from radioiodine therapy are also probably unlikely.

Discussion and Conclusions. Radioactive iodine, half life 8 days, has been used 47 times in the treatment of the 40 cases of hyperthyroidism at the Presbyterian Hospital included in this report. Twenty-seven of these responded favorably to a single dose. Seven of the 13 failures with one dose were given a second treatment and 3 more responded favorably; the remaining 6 cases have been retreated too recently to report. Thus of the 34 cases given a single dose, and when necessary a second, 30 were put into remission (88 per cent) as judged by a follow-up period of 4 months or more. This success rate is especially striking since half the cases were recurrent toxic goiter after operation, and were uncontrollable by other methods of therapy. The series is small as yet, and further data are necessary before a final evaluation of the method can be made.

The factors pertaining to the failure of therapy have been discussed. It appears that when an adequate amount of radioiodine is administered, as determined by the percentage uptake and the size of the gland, a relatively high percentage of successes should be expected. A dose of 100-150 uc per gram of thyroid weight administered, or of 50-75 uc per gram retained seems adequate. A radiation dose of about 6000 equivalent roentgens appears to be the desirable level. The problem, of course, is to select a dosage which will control the toxicity, but not induce gland underfunction and permanent hypothyroidism.

The success rate here reported compares well with that of surgery (90 per cent) and surpasses the results of x-ray therapy (80 per cent) and of thiouracil and propyl thiouracil treatment (about 60 per cent in primary goiter, 10 per cent in recurrent goiter).⁶ Surgery provides relief

in a shorter time than the two or three months usually needed to induce remission with radioiodine, but has the objections attendant on operation. Antithyroid drug therapy may take one or two years, without assurance of success, but has few complications, and little question of cancer formation later. In view of the remote chance of late malignancy following radioiodine therapy, most workers in this field agree that such therapy is still too new for general use, and that it should be employed only in those centers where adequate follow-up is available, where careful measurements of dosage can be carried out, and where strict precautions against radiation hazards from the handling of the iodine can be maintained.

Complications have not been severe and no instance of permanent hypothyroidism occurred in the present series. The presence of cardiac failure, a rare event nowadays, may be a complication prior to radioiodine treatment preventing its immediate use, due to the uncertain success which follows a single dose and to the 3 months interval until success or failure can be determined. However, even with failure, the patients are usually greatly improved. Finally, malignant exophthalmos has not occurred in this series. However, if the mass of gland tissue is a factor in inhibiting the appearance of this condition, the destruction of gland tissue by radioiodine contraindicates its use where this is a likely possibility. This point remains to be settled.

SUMMARY

1. Radioactive iodine of 8-day half life, I^{131} , has been used in tracer studies of iodine uptake by normal and disordered thyroid glands, and in the treatment of 40 cases of toxic goiter.
2. Tracer uptake has diagnostic value, when stable iodine or anti-thyroid drugs have not been given shortly before this procedure. Normal uptake is 20-30 per cent of the administered tracer dose of 50-75 uc. Anything more than 40 per cent is regarded as definitely hyperthyroid, anything less than 10 per cent as hypothyroid.
3. Therapy has been successful in 30 of 34 cases after one, or when necessary two doses, with four failures. Six other treated cases did not respond to one dose, and have not been followed after a second long enough to draw conclusions.
4. The causes of failure in the present series have been analyzed; they appear to be due to inadequate dosage, related mainly to the size

of the gland. It is possible that an unusually high basal metabolic rate may also contribute to an unsatisfactory result.

5. The complications following radioiodine therapy include sore throat, cough, tender gland, flare-up of toxicity, and transient hypothyroidism. Only a few cases of each have been observed; none of them was serious.

6. Radiation hazards attendant on this therapy are analyzed; under the present conditions they are unimportant.

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THE ORGANIZATION OF CARDIOVASCULAR FUNCTION*

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THE FUNCTION OF THE CARDIOVASCULAR SYSTEM

THE IMMEDIATE environment of the cells in lower organisms varies with remote changes over which the organism has no control. In multicellular organisms, however, the situation is different; the cells are bathed in a fluid which tends to resist the commonly occurring environmental changes because of the character of its physical and chemical properties.

In the larger metazoa the importance of a stable environment for the cells is so great that mechanisms have developed which provide for a constant renewal of the intercellular fluid. In man this is accomplished by the continuous filtration of fluid from the blood stream into the extravascular spaces and its return by way of the capillaries and lymphatics.

Apparently the complexity of the cardiovascular system has evolved in response to the difficulty of providing a proper amount of fresh fluid to the tissues and to the organism's dependence on the adequacy of this provision. The prime function of the cardiovascular system, therefore, is to assure a rapid turnover of tissue fluid in amounts adapted to the activity of the various parts of the body.

A brief review of the general mode of operation of the cardiovascular system should consider first the formation of tissue fluid.¹ An unselected fluid of low protein content is filtered from the blood partly through the endothelial cells of the capillaries and partly through the cement substance which joins them. The rate of filtration depends on the pressure within the capillary, on the permeability of its wall and on the forces tending to oppose the extravasation of fluid. This fluid is

* Based on two of a series of three lectures delivered at New York University, December, 1946.

normally returned to the blood by a force resulting from the pressure in the tissue spaces and the osmotic pressure of the proteins remaining in the plasma. Some components of extravascular fluid, especially protein and particulate matter, return by way of the lymphatics.

To serve these ends are the capillaries—thin-walled tubes whose patency varies with the rate of metabolic activity of the tissues which they supply. The pressure within the capillaries forces the blood on through the venules into the great veins and so to the heart. The continual movement of the structures in which the veins are embedded helps to move the blood forward since it is prevented from returning by the arrangement of the valves. Thus the veins are continuously emptied and the outflow from the capillaries is facilitated.

All the blood which is returned to the heart is pumped through the pulmonary circuit and then expelled into the aorta which being elastic serves as a reservoir to contain at all times enough blood under pressure to supply the demands of the tissues. The long arteries deliver the blood to various organs; there the arterioles serve as shutoff valves which maintain the blood pressure since they relax only enough to deliver the blood immediately required by the tissue in which they lie.

The central feature in the mechanism for assuring a turnover of tissue fluid adequate to maintain a constant environment in regions of active metabolism is the fitness of the cardiovascular system to deliver a large amount of blood at high pressure.

The usual description of the circulation presents the heart and medulla oblongata as directing the cardiovascular system to supply blood where and when it is needed; the physical, endocrine and higher nervous aspects of cardiovascular regulation being interesting addenda to the main story.

The chief intent of this lecture is to consider the cardiovascular system from a different point of view. The cardiovascular system will be treated as a mechanism on which *each tissue may make demands that will be automatically supplied* within the limitations of the system. The system is self-adjusting and self-compensating for the ordinary loads put upon it through a combination of physical, chemical, and medullary reflex controls. The hypothalamus biases or guides these automatic adjustments in such a way as to integrate the requirements of various body functions and to provide for special needs related to changes in the external environment. All of these adjustments are to a greater or lesser

degree subject to modification by endocrine activities called into play by common emergencies.

A brief review of the history of our knowledge of the cardiovascular system will show how the heart came to be erroneously considered as the master of the circulation and why only recently attention has been focused on the capillary which is the true functional center of the cardiovascular system.

HISTORICAL REVIEW

From the earliest times the heart has been correctly recognized as of supreme importance. Men observed the presence of the apex beat in the chest and its cessation at death; the dramatic and usually fatal results of wounds involving the heart further accentuated its importance.

The foundation of modern analytical physiology was laid in 1628 with the publication of Harvey's book, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*.² The title, together with the evidence presented, still further accentuated the central importance of the heart. Thus enthroned, the heart ruled our concepts of the cardiovascular system with a progressively heavier hand until well into the present century. Harvey recognized that the blood in the arteries is under pressure (Chapter 3) and that the quantity of blood expelled by the heart varies from time to time (Chapter 9). He promised to report measurements on cardiac output but this promise was never fulfilled nor have any notes of such experiments been found. We are now beginning to recognize that these two measurements—blood pressure and cardiac output—are necessary for a rational understanding of the behavior of any particular heart.

Soon after Harvey's publication, the early microscopists described the capillary bed without apparently realizing that this was much more than the link in the chain which completes the circulation. The next dramatic advance in our knowledge of the physiology of the cardiovascular system was the publication of Stephen Hales' work on hemostatics³ which gave the first measurements of blood pressure and described its pulsations and their relationship to the heart beat. Here again the accident of experimentation continued to place emphasis upon the heart.

During the early nineteenth century the recognition at autopsy of hearts grossly enlarged by dilatation or hypertrophy and their relation-

ship to what we now recognize as heart disease on the one hand and Bright's disease⁴ and essential hypertension on the other continued to keep the emphasis where it had been before.

This emphasis led Fick⁵ in 1870 to explore the relationships now known as the Fick principle and to point out that if quantitative experimental techniques were available it would be possible to determine the cardiac output accurately from the oxygen utilization of the whole organism and the difference in oxygen content between the arterial and venous blood. It was some years before the Fick principle was used for the determination of cardiac output in experimental animals and it is only quite recently that it has come to a full fruition with the development of the techniques which make it applicable to man. The practical value of the Fick method of measuring cardiac output in man seems to have diverted attention from the very important theoretical implications of the Fick principle.

In the middle and later parts of the nineteenth century, physiologists showed great experimental ingenuity and skill in the design and construction of instruments for the registration of small mechanical changes. Their techniques, the new availability of anesthetics and the increased number of persons trained and interested in technical procedures which followed the industrial revolution combined to stimulate research. All phases of physiology underwent a rapid increase in the rate of accumulation of factual knowledge; and because of the mechanical techniques available, this knowledge in the field of cardiovascular physiology was directed mainly to the heart and great vessels since these structures are large and readily accessible.

At the turn of the century, when Riva-Rocci⁶ introduced the sphygmomanometer, the accumulated information about arterial blood pressure, obtained mainly from anesthetized animals, became directly available for use in clinical medicine. The electrocardiograph which readily gives the clinician information about the heart, precise to thousandths of a volt and hundredths of a second, still further spotlighted the heart.

The pioneer studies of Elliott⁷ on the vascular properties of extracts of the adrenal medulla and those of Dale⁸ and of Kamm⁹ on the pressor principle from the pituitary body provided the factual beginnings for our present views of the endocrine control of the cardiovascular system.

In the light of this historical review it is understandable that the cir-

culation came to be thought of as a heart and arteries, which, under the control of the medulla, forced blood at pressures determined by the vasomotor centers through arterioles into capillaries whose state of dilation is to some extent controlled by local metabolism.

Knowledge has also accumulated about a variety of other phenomena in cardiovascular physiology. These include reflexes controlling the circulation, endocrine substances which affect the arterial blood pressure, the influence of pain, emotional excitement and other states transmitted from the higher centers to the cardiovascular system, as well as the behavior of the system in response to various emergencies such as shock, hemorrhage, violent exercise and extremes of heat and cold. As might be expected attention was focused on the heart and great blood vessels which were easily accessible to study rather than on the peripheral circulation and capillaries which are the principal reason for the existence of the cardiovascular system.

During the first quarter of this century Starling¹⁰ isolated first the heart and then the heart and its connections with the medulla from the rest of the cardiovascular and nervous systems. It then became evident that the heart and its immediate connections were so organized that, within wide limits, this system would expel as much blood as came to it by the veins against whatever pressure obtained in the aorta.

This self-regulating system consists of the heart (including myocardium, conduction system, and coronary circulation), the medulla oblongata and the reflex circuits from the great veins, pulmonary arteries, aortic arch and carotid bifurcations, which pass through the medulla and back to the heart by way of the vagus and sympathetic nerves. Starling emphasized that there was nothing within the heart and its nervous connections which determined the work which it would do either in point of quantity of output or of pressure, but that the activity of the heart and its accessories was determined from without by the demands of the other parts of the body, as expressed by the venous return and the aortic tension.

This *dethronement* of the heart from the position which it had occupied in the minds of most writers as the central determiner of the circulation was so radical that its full significance has been accepted only very slowly by physiologists. Those who have devoted critical attention to clinical cardiology have had an even harder time than the physiologists in convincing their colleagues of the necessity of recog-

nizing that the behavior of the heart is determined by the demands made upon it and that the heart does not determine the activity of the peripheral circulation except in cardiac failure.

Damage to the heart, mild or severe, acute or chronic, chemical or biological, gives signs in the peripheral circulatory system only when the load put upon the heart is so great that the damaged heart can no longer sustain the load and begins to fail. In Stokes-Adams syndrome the cardiac arrest causes a complete failure of the heart to pass the blood on to the arterial system so there is a fall in blood pressure and syncope. In congestive heart failure, even in its earliest stages, the presence of edema, dyspnea and other effects of raised venous pressure suggests that the heart is failing to remove all the blood from the veins.

If we consider earlier stages of those processes in the myocardium which ultimately lead to failure we find little evidence that mild impairment of the heart affects the delivery of blood to the tissues, for there is no change in blood pressure nor in resting cardiac output. It is true that the cardiac reserve is impaired; whereas a normal heart may respond to violent exercise by a nine-fold increase in output even against a raised aortic blood pressure, a slightly damaged heart will show signs of failure to sustain the extra load of moderate exertion. Ordinarily in patients with conduction defects or errors of rhythm shown solely by the electrocardiogram, this failure to meet an extra demand is demonstrable only when the cardiovascular system is subjected to severe stress. In many acute coronary attacks, however, the blood pressure falls rapidly during the first hours or days; the decline of blood pressure is said to be due to the weakness of the myocardium. This explanation is probably true in severe coronary attacks but in minor attacks the fall of blood pressure may be due in part to a combination of the relaxation of the arterial system from the diminution of the pain and from the influence of the sedatives used, and to the fact that the enforced sedation and rest have so lowered the tissue demands for blood that the blood pressure falls rather for lack of demand than because of lack of available driving force.

One still hears of a pulse acceleration speeding the circulation or making the heart work harder, or of the force of the heartbeat determining the arterial blood pressure. Starling, on the contrary, showed that increased force of beat is due to raised aortic pressure. Similarly, when the total blood flow and aortic pressure are so great that the heart

might be faced with an inordinate amount of work per beat, we see the Bainbridge accelerator reflex in operation. This causes the heart to beat more frequently when there is more work to do. Acceleration by itself probably affects the venous return, the cardiac output (minute volume) or the arterial blood pressure chiefly when the heart is close to physiological failure.

During the 19th century the details of the peripheral circulation were receiving considerable attention. One may mention only such highlights as the many studies of various aspects of vasomotor control; the work of Gaskell¹¹ who saw the local dilating effects of metabolites but failed to establish for this discovery the importance it now has; and Starling's description of the formation of tissue fluid and the nature of its demands on the capillary circulation. Details of the behavior of the capillaries and their adaptation to the demands for tissue fluid were elucidated largely after the turn of the 20th century by the work of August Krogh¹² and by the studies of Sir Thomas Lewis¹³ upon the minute vessels of the human skin. More recently this work has been extended by Chambers and his collaborators.¹⁴ The physiology of the capillaries and of tissue fluid formation now appears to be receiving the attention which it deserves.

The cardiovascular system is still commonly visualized as a heart and arteries, which, under the control of the medulla, force blood at pressures determined by the vasomotor centers through arterioles into capillaries whose state of dilatation is to some extent controlled by local metabolism. After giving rise to tissue fluid this blood is returned by the veins to complete the circulation.

It seems possible at this time to improve our general understanding of the circulation by considering, first, the supply of blood to the capillaries in response to local demands; secondly, the endocrine mechanisms which integrate cardiovascular activity to meet stereotyped emergency situations; thirdly, the self-regulating arrangements whereby the medulla, heart, and great vessels work together in a self-compensating fashion to provide a continuous and almost inexhaustible reservoir of arterial blood at high pressure; and finally, to consider those phylogenetically recent and individually acquired mechanisms whereby unexpected external events and emotional states may make appropriate modifications in the behavior of the cardiovascular system.

PHYSICAL REGULATION OF CARDIOVASCULAR FUNCTION

The regulation of the cardiovascular function, that is, the adaptation of its various parts to momentary changes in the internal and external environments, like the regulation of many other important physiological functions, seems to depend basically upon the physical structure of the system and the effect on it of physical changes in the environment. It is this basic automatic physical regulation that the chemical and nervous mechanisms modify. For this reason the physical aspects should be first considered. Since the knowledge of cardiovascular physics is still very patchy, a few illustrative examples of these physical considerations must suffice.

Capillaries: In all organisms a rise of temperature, whether transmitted from without or generated within, is accompanied by an increase in metabolic rate and in the diffusion currents by which the metabolic needs are satisfied. In the mammal the arteriole and capillary are the keys to the turnover of tissue fluid and thus to the constancy of the internal environment. These structures relax when the temperature around them increases and thus allow more blood to flow to the warmed part. This is true whether the warmth is due to increased metabolic activity of the cells in the neighborhood, or, as in the case of the skin, to warmth from without.

The result of mechanical stimulation is another interesting example of the physical regulation of the circulation. In nature a mechanical stimulus is the warning or actual forerunner of impending injury and the vasoconstriction which it produces may sometimes serve to diminish the loss of blood. This vasoconstriction from mechanical stimulus is a well-known laboratory phenomenon and may be observed in arteries, veins, and in the capillaries of the skin. The development of other and presumably more effective chemical and nervous reactions to injury has masked this reaction so that in man at present it appears to be somewhat vestigial, but we should remember Barcroft's¹⁵ warning against dismissing observations whose meaning is obscure. "Accidents happen in nature as elsewhere, but—I range myself on the side of those that regard a phenomenon as more likely to have a significance than not. Those who think with me must shoulder the burden of discovering what the significance may be, but on our opponents rests the much heavier burden of proving the phenomenon to be an accident if indeed it be such."

Some other examples of the physical regulation of the circulation may be found in the physiology of the veins, the heart, the pericardium, the great arteries and the blood.

Veins: The respiratory pump and the massaging action of the muscles are the best known of all the physical means of modifying the venous return in accordance with the metabolic activity.

Heart: Starling's law¹⁶ suggests that the fundamental structure of the heart is responsible for adjusting its activity in response to the physical effect of distension, and so adapting the amount of energy produced to the work necessary to maintain the circulation of the blood coming to the heart. Cardiac muscle, like skeletal muscle, is so constructed that a physical condition (the length and tension of the fibers) determines the amount of energy which will be released at its next contraction. The diastolic volume of the ventricle is determined principally by the arterial tension at the end of the previous systole and by the venous return during diastole. In this way, since the factors determining the work of the heart determine also its volume at the end of diastole, the energy discharge in systole is automatically regulated in accordance with the amount of work to be done.

All muscles have such a mechanism for adjusting their activity to the work they must do. In the case of the heart, however, the Bainbridge accelerator reflex further extends the ability of the organ to accept increased loads without failure. The venous return and the aortic pressure set the task for the heart. These factors adjust the heart's ability to perform the task by the means just discussed.

Pericardium: The principal function of the pericardium is to set a physical limit to the stretching of the heart and thereby to minimize the chances of functional valvular incompetence and muscular rupture. Yas Kuno¹⁷ concluded that the pericardium does in fact restrain venous filling. He found that slitting the pericardium increased not only the maximum diastolic volume but also the maximum work output obtainable from a heart-lung preparation. Wilson and Meek,¹⁸ using an X-ray method and thus avoiding the use of the open-chest preparation, confirmed this conclusion.

Windkessel: The great arteries or windkessel are primarily concerned with the acceptance of the systolic discharge of blood and its delivery to the tissues during diastole. Evidence is accumulating that its capacity and rigidity may change rapidly in a direction which tends

toward the preservation of the *status quo*. The mechanism of this change is disputed. As the blood pressure rises, the windkessel becomes more rigid and thus resists further distension. This is to be expected from the elastic behavior of many similar structures. The question at issue is whether or not there is a specific mechanism for rapidly changing the elastic properties of this structure comparable with the elastic changes seen in muscular contraction.

Any non-rigid container can accommodate to additions to its contents by stretching in response to an increased internal pressure. The relationship between the pressure applied and the increase in capacity or between the stress and the strain may be plotted. The result represents the elastic property of the structure. With a few exceptions, which the physicists refer to as "perfectly elastic bodies," such a graph is a curve indicating that within limits the more a structure is stretched the more difficult it is to stretch it further. This property is recognized beyond doubt in the aorta just as in other tissues. Skeletal muscle and probably other muscles also are characterized by the fact that this elastic curve for relaxed muscle differs importantly from that for contracted muscle. There has been some controversy as to whether the aorta, like muscle, can exhibit such rapid changes in its elastic properties.

Wiggers and Wégris¹⁹ recorded the simultaneous changes in aortic pressure and aortic diameter of dogs subjected to acute pressor effects of epinephrine, pitressin, "vagus stimulation" and asphyxia. In each case, as the pressure rose the aorta first expanded, then shrank, and finally exhibited an increased distensibility. This is exactly what would be expected if the aorta were a vessel of pure muscle and responded to the rise of pressure by contraction and to the subsequent fall by relaxation. Exact analysis of the data is difficult since there is a slight lag in the aortic response, but the above interpretation of the findings is in essential agreement with Wiggers.

Blood: The inherent homeostatic nature of blood was most completely presented in L. J. Henderson's book²⁰ "Blood, a Study in General Physiology" which J. S. Haldane²¹ aptly discussed as "Blood, a Study in Physical Chemistry." Blood, even on the more strictly physical side, is a remarkably "self-regulating" fluid as is illustrated by the effects of changing blood viscosity. The principal variation in viscosity is due to changing red cell count. One of the important consequences of this is that anemic blood, which carries less oxygen per cubic centimeter

than normal blood, can pass more easily through the vascular system because of its lowered viscosity, and thus deliver more oxygen per minute than it otherwise would.

These examples show that much of the organization and regulation of the cardiovascular system is inherent in the physical character of its ingenious structural arrangements.

CHEMICAL REGULATION OF CARDIOVASCULAR FUNCTION

The control of the distribution of blood is mainly by chemicals produced by the tissues concerned. The essential relationship of these substances to blood distribution is often overlooked. The chemicals now under discussion are quite distinct from the hormones and for convenience of discussion we may make an incomplete separation between those whose cardiovascular actions occur near their site of production and those whose action is central or general.

Chemicals with Local Action: Gaskell²¹ in 1877 was the first to recognize the vasodilator properties of the acid products of metabolism and their importance in increasing the blood flow through active tissues. Half a century later a revival of interest in this subject led to its study by newer methods in many laboratories. Anrep,²² summarizing the work to which he and his colleagues so largely contributed, showed clearly the quantitative connection between the activity of a tissue, its ability to alter the composition of the blood flowing through it, and the rapidity of its blood flow. Blood collected from an active limb and then perfused through a resting limb consistently increased the blood flow. This was a complete quantitative establishment of the concept that the chemical products of metabolism control the flow of blood; moreover, muscular activity produces a greater blood flow than does ischemia. Anrep was inclined to attribute the greater part of this effect to histamine. Excess carbon dioxide or lack of oxygen could be made to imitate the "activity" effect both in intensity and time scale, but either a lack of oxygen or an excess of carbon dioxide was invariably accompanied by an excess of histamine in the venous blood.

The specific products of metabolism which are known to be vasodilators include hydrogen-ion, carbon dioxide, lactate-ion, phosphate, adenosine and related compounds²³ and histamine. To these metabolites may be added diminished oxygen tension.

A large literature on the vasodilator properties of each of these

metabolites indicates uncertainty as to their efficacy in the concentrations which may be expected at the actual site of production. Acidity, histamine, and adenosine triphosphate, however, are strong vasodilators and are probably effective even in the concentrations involved in mild activity, especially if reinforced by carbon dioxide and lactates.

The rise in hydrogen-ion concentration which occurs in active tissues breaks down an inactive compound liberating kallikrein which further adds to the accumulating vasodilator environment.²⁴

A sufficient accumulation of metabolites can produce a maximal blood flow of a magnitude quite different from the increases produced by the nervous system, by acetylcholine (which is abundantly liberated in an active muscle), or by the ergotoxine-epinephrine sequence.

Much more investigation is needed to elucidate the relationships and relative importance of these various vasodilator influences; but it is quite clear that locally liberated chemicals provide, for any tissue that becomes active, a large increase of blood supply. This depends only upon an adequate reserve of arterial blood at a sufficient pressure and is independent of specific nervous or endocrine regulation.

There are many other vasoconstrictor and vasodilator substances extractible from blood and tissues which have not been sufficiently studied to enable us to distinguish between the pharmacological accidents of the extraction process and substances which may have physiological meaning.

Chemicals with General Action: Carbon dioxide is one of the most interesting and controversial chemicals from the cardiovascular point of view. This substance probably acts locally at its point of generation, as do other metabolites, to produce vasodilation and increased local blood flow; but as the blood bearing this excess carbon dioxide passes into the arterial system it acts centrally and may produce a generalized vasoconstriction. This state of vasoconstriction tends to divert the blood from regions which are not actively metabolizing to those which are, and at the same time tends to maintain or even elevate the blood pressure in the face of the extra drain produced by the metabolic requirements of the active region. This central vasoconstrictor action of carbon dioxide is, in part at least, a reflex originating from the aortic and carotid bodies. Carbon dioxide in the blood stream has further effects upon the heart rate and the coronary system. These effects are fairly well described, but their importance in the integration of cardiovascular activity with

the activity of the tissue producing the carbon dioxide needs further clarification.

Because it is the best known, carbon dioxide has been taken as the chief example of the substances which act usefully at a distance from the site of their origin but fail to fit into the usual concept of hormones. Further, it illustrates a common and paradoxically useful occurrence. Where carbon dioxide causes local vasodilation and general vasoconstriction, two diametrically opposite mechanisms work toward the same end—that is, more blood flow to the site of production of carbon dioxide.

The lactate-ion provides another useful illustration of the chemical integration of the cardiovascular system. As a vasodilator¹¹ produced during muscular activity, it makes an extra demand on the heart. If produced in sufficient amount significantly to raise the lactate content of arterial blood, it provides a readily available fuel for the heart.

The chemical regulation just discussed serves to ensure that each part get a blood supply in accord with its activity. The complexity of the organism, however, is such that an excessive demand made simultaneously by two different organs might cause a breakdown of the whole system. One organ even might so tax the system that some vitally and immediately important function would not be properly served.

ENDOCRINE INTEGRATION OF CARDIOVASCULAR FUNCTION

The chemical and physical controls of local origin are therefore in a sense anarchistic. If many tissues simultaneously become active and by their local mechanisms preempt a large blood supply, the demands may exceed the capacity of the cardiovascular system; but endocrine and nervous mechanisms regulate the parts of the cardiovascular system so that they continue to function harmoniously even in the presence of extreme demand. These mechanisms so integrate the blood supply to different parts of the body that non-essential functions shall not dangerously divert blood from essential or emergency functions. The maintenance of harmony within the cardiovascular system seems to be mainly a medullary function; the adjustment of cardiovascular activity to the needs of different parts of the body and to external events is mainly handled by endocrine means and by the higher parts of the brain.

Certain emergencies such as trauma, shortage of water or minerals, or the need for sudden exertion recur frequently in the history of an

individual or species. These emergencies seem to excite endocrine mechanisms which integrate the local demands with requirements of the whole organism.

The Renin Mechanism: A variety of frequent natural accidents which occur in all species and threaten life produce a diminution of pulse pressure, a rapid pulse rate and a diminished plasma volume. In such conditions, as for instance hemorrhage and shock, the threat to life is tissue anoxia. Since the circulating blood volume may become too small to fill the vascular system, the heart is inadequately filled, the cardiac output drops and the blood pressure falls to a level where it fails to force enough blood through the coronary and cerebral blood vessels to sustain life. In these disastrous states where death is imminent, all the available mechanisms—physical, endocrine, and nervous—come into play to maintain the failing circulation.

Here, however, I wish to analyze the first minor deviations from the normal physiological state and the mechanisms which are usually successful in counteracting them. In trauma, pain accelerates the heart and by sympathetic excitation tends to diminish the lumen of the renal arteries. Loss of blood—either by external hemorrhage, bleeding into dilated capillaries, or excessive transudation of fluid through the capillary walls—tends to diminish the systolic output both by defective diastolic filling and by reflex cardiac acceleration. So, on many counts, we may expect the force of the pulsations delivered to the renal parenchyma to be diminished. This diminution, perhaps by interfering with the normal expansile pulsation of the kidney²⁵ is followed by an immediate liberation of renin into the blood stream. The delay in this reaction is probably negligible, for the liberation of renin has been demonstrated within four minutes of the stimulus.²⁶ Probably the change in pulse pressure necessary to produce an effect is very small.²⁷ If the amount of renin liberated is small, the most striking effect is a constriction of the efferent glomerular vessels of the kidney.²⁸ This increases the fraction of plasma filtered off by the glomerulus and thus enables the elimination of soluble wastes to be maintained even though the blood flow through the kidneys is diminished. A somewhat larger liberation of renin causes a more generalized vasoconstriction together with splenic and venous contraction, and perhaps, also, a cardiotonic effect. All these effects tend to prevent the blood pressure from falling as the effective blood volume diminishes. That this mechanism fails in fatal shock and hemorrhage

through exhaustion of the renin-substrate²⁹ and probably, also, through exhaustion of the kidney,³⁰ is perhaps evidence that it has been useful in the minor and non-lethal disturbances.

That renin may, in fact, be liberated promptly by a normal kidney and may contribute to vascular homeostasis is based securely on a wide variety of experiments.

The anesthetized animal's blood pressure will rise within fifteen minutes of appropriate interference with its renal blood supply. This has been shown to be due to the release of renin.³¹ Hemorrhage or injection of Nembutal^{26, 27} will cause the immediate liberation of renin.

The intimate nature of the stimulus to renin secretion is still controversial and of much interest. Goldblatt³² and those who followed him in this field, at first believed hypertension from renal artery compression was due to renal ischemia. "Ischemia" is apparently used here to mean a deficit of blood supply relative to the work done. Considerable evidence suggests that this view is incorrect. Dock and Rytand³³ using the method of partial nephrectomy in rats showed that the renal stump of a rat made hypertensive by this method did not carry less blood per gram of renal tissue. A large arterio-venous oxygen difference is generally regarded as a characteristic of ischemia. No change has been shown in the arterio-venous oxygen difference of the "ischemic" kidney.³⁴ This is not conclusive evidence, however, that the blood supply is enough; there might be insufficiency of some substance other than oxygen. Corcoran and Page,³⁵ using clearance methods, showed that some hypertensive Goldblatt animals did not have a diminished renal blood flow.

On this evidence we may accept for the present the concept that there may be some factor other than ischemia concerned with producing these changes. After Page³⁶ had demonstrated that a similar hypertension followed the perinephritis which developed around a kidney wrapped with silk or cellophane, the question arose, "Does this perinephritic capsule restrict the blood flow?" The answer to this is now known to be "Not always."³⁵

Kohlstaedt and Page³⁷ demonstrated the liberation of renin by a kidney which was perfused with a pump-lung preparation. With the pulse pressure occurring in their circuit, they found no renin in the blood leaving the kidney. When they applied a clamp to the hose taking blood to the kidney, renin was promptly liberated in measurable amounts even though the blood flow through the kidney was not al-

lowed to diminish. This very important experiment has not received the enthusiastic acceptance it might deserve because of the obvious possibilities for error in so complicated a procedure. The methods for assay of renin in blood, still lamentably unsatisfactory, were at that time open to very grave doubt. The pulse-wave form and pulse pressure of a pumping-lung preparation are determined by the specifications of the glass and rubber and are of evident importance in these experiments, but it is difficult to reproduce the experimental conditions exactly. Nevertheless, it seems reasonably certain that the principal change associated with the liberation of renin in this experiment was, in fact, a change in pulse pressure.

The concept that pulse pressure rather than ischemia determines the liberation of renin is of great importance. Since it was originally based on experiments involving so much technical skill and difficulty that nobody has yet repeated them, I may mention some other experiments which bear indirectly on this point. The importance of these experiments was not recognized since they were performed long before the recent revival of interest in renal hypertension.

A number of years ago I had the privilege of helping Dr. Bayliss³⁸ with a perfusion of some dog kidneys in a study of renal excretory mechanism. For convenience in the perfusion circuit we were using a high speed rotary pump³⁹ which gave about 800 pulsations per minute. In this circuit the pulse pressure must have been exceedingly small. Difficulty was experienced in forcing enough blood through the kidneys at a reasonable pressure, partly because of the well-known vasoconstrictor properties which shed blood may acquire, and partly, maybe, because of the liberation of renin by perfusion at a very low pulse pressure. We later found that the same circuit, equipped with a reciprocating pump giving approximately physiological pulse rate and pulse pressure, would allow adequate perfusion.

Many of the experiments demonstrating renin in the blood of the whole animal in response to what are usually spoken of as "hypotensive" stimuli further bear out the concept that the pulse pressure is the determining factor in the liberation of renin, though none of these experiments seems to provide critical evidence on this point.

The question therefore arises, can perinephritis affect the pulse pressure of the blood delivered to the kidney? This would be difficult to determine experimentally and no measurements have yet been re-

ported. Theoretical considerations suggest that if the kidney is rigidly splinted by experimental encapsulation the pulse pressure within it would be unchanged or might be somewhat increased though the magnitude of this increase would probably be negligible. It is unlikely that the kidney can distend and collapse to its normal degree with systole and diastole if it is encased in a rigid capsule. This would also be true if the pulse pressure delivered to a normal kidney (without perinephritis) were too small to produce the normal degree of expansile pulsation.

It appears that whenever renin is liberated the dynamic situation is such that the expansile pulsation of the kidney is diminished, but no critical experiments have yet been reported to prove a causal relationship even though this seems to be the only single relationship which will account for the generally accepted facts.

At the risk of theorizing on an imperfect foundation we may point to the facts that there are other organs which depend upon rhythmical movement for their well-being and that the elimination of tissue fluid, particularly by way of the lymphatics, is largely dependent upon physical movement of the organ concerned. Such factors might conceivably be concerned with the liberation of renin.

Space does not allow a detailed account of all the work which has been quoted for and against the view that the production of renin is a defense mechanism against blood volume deficit. It is sufficient if this account directs attention to the possibility that the kidney may be important in a certain group of cardiovascular emergencies.

The Posterior Lobe of the Pituitary Gland: A common emergency is that of water shortage which is met in part by the posterior lobe of the pituitary gland from which may be extracted a chemical, vasopressin (Pitressin), whose actions are three-fold. Vasopressin excites most smooth muscle in the body, it contracts capillaries and it promotes the reabsorption of water by the distal uriniferous tubule thus producing an antidiuretic effect.

Studying the antidiuretic properties of vasopressin, Gilman and Goodman⁴⁰ have shown that shortage of water is an appropriate stimulus to the liberation of this substance. They found that the rate of excretion of antidiuretic hormone in the urine was greater in those rats which had been dehydrated by lack of water or by hypertonic saline than in those which had been hydrated by the administration of excess water. It is evident that in such circumstances when the need for water

conservation is important this same substance is useful in its ability to mobilize blood by the constriction of capillaries and veins of the cutaneous and splanchnic areas.

The first activity of this substance to be recognized was its power to raise the blood pressure of anesthetized animals by peripheral arterio-lar and capillary constriction. Thus it received its name "vasopressin." A careful study of its antidiuretic properties, however, has shown that this substance will produce antidiuretic effects in quantities far too small to have any detectable effect upon the blood pressure. For this reason there has been some question whether its blood pressure raising effect has any physiological significance and, in fact, Gilman and Goodman and others have even questioned whether injection of vasopressin raises the blood pressure of normal, unanesthetized man. However, after a careful consideration of the effects, Van Dyke⁴¹ in his monograph of 1939 agrees with Schockaert and Lambillon⁴² and others who claim that vasopressin injected intravenously will raise the blood pressure in man. This difference of opinion serves to emphasize the fact that the pressor activity is comparatively weak and therefore difficult to study.

Since the pressor action can be demonstrated, it is necessary to inquire whether it is a pharmacological accident or whether the effect occurs when the gland *in situ* is activated naturally. Excitation of the central end of the cut vagus can produce a sufficient liberation of posterior pituitary hormone to raise the blood pressure⁴³ but the proper physiological excitation of the vago-hypophyseal reflex has not yet been accomplished. The pressor activity of the pituitary gland may nevertheless be as physiological as its antidiuretic activity. If this be so, vasopressin acts not on one organ (the kidney) but on a variety of organs whose functions may be coördinated to meet the common emergency of water shortage. Vasoconstriction and antidiuresis would both serve the same end. This regulation of a single function of one substance which acts on a variety of mechanisms seems to be characteristic of the endocrine system.

The Adrenal Medulla: The recognition of the adrenal medulla as an endocrine organ for mobilizing all available resources for "fight or flight" was clearly established by the well-known work of Cannon.⁴⁴

Violent excitation releases epinephrine which mobilizes blood by contraction of the spleen and the mesenteric veins. This action empties about a liter of cell-rich blood into the general circulation.⁴⁵ By con-

traction of the vessels in the plexuses of the skin another 500 cc. or so of blood is forced into the general circulation. And, finally, contraction of the splanchnic and cutaneous arterioles diverts the circulation from these regions to others of greater activity helping to maintain or raise the blood pressure by increasing the peripheral resistance. The increased blood volume tends to raise the venous pressure and distend the heart thereby raising the cardiac output and further helping to maintain the blood pressure. This is achieved in spite of an increasing demand for blood which is associated with widespread arterial relaxation in active parts of the body. The increased flow through the muscles still further adds to the venous return. That the venous pressure does not become inordinately high in these circumstances is due in part to three further actions of epinephrine. It acts on the pacemaker of the heart, increasing the rate and thus the number of rapid-filling periods per minute; secondly, it acts in a positive inotropic fashion,⁴⁶ increasing the power of a well-filled heart to empty itself rapidly and completely against a high blood pressure; and thirdly, it dilates the coronary arteries⁴⁷ and provides more oxygen for a hard-working heart.

In this way epinephrine not only increases the load of the heart but also increases its power to carry the load. The enormous increase in pulmonary blood flow⁴⁸ (approximately nine-fold) which occurs in these circumstances tends to produce a very high pulmonary arterial pressure. The pulmonary vessels, only lightly supported by the spongy parenchyma of the lungs, distend in response to this pressure and so more easily permit the increased quantity of blood to pass. The excessive distention of the pulmonary vessels, which might lead to rupture, is in part counteracted by the fact that epinephrine decreases their distensibility.⁴⁹

This brief review of a few of the cardiovascular effects of epinephrine could be extended by a discussion of its possible effects on the aorta and the arteries within skeletal muscle, on the respiratory tract, and on metabolism and digestion. All these well-known actions of epinephrine support the concept that the adrenal medulla, like other endocrine glands, produces a secretion which helps to meet certain general situations rather than a substance specialized to act on any particular kind of tissue. The clearest cases in point are its widely differing action on the arterial muscle in the heart and in the gut, and the contrast between its inhibitory action on the digestive glands and its secretagogue action on the sweat glands.

The general concept of the emergency action of epinephrine has long been current. This has tended to obscure the fact that it is but one of the endocrine mechanisms organized to meet but one kind of emergency. The endocrine mechanisms for other emergencies have been studied more recently and less completely.

The Adrenal Cortex: A word must be said about the adrenal cortex as a cardiovascular organizer against stress on salt and water metabolism. Detailed information is accumulating so rapidly that no immediate attempt should be made to analyze this function rationally. However, the following simple points will bear pondering. The importance of the proper activity of the adrenal cortex in maintaining normal cardiovascular function is clearly shown by the diminished blood volume and lowered blood pressure in Addison's disease and perhaps also by the hypertension of Cushing's syndrome. The exact mechanisms involved are not clearly understood, nor is the nature of the environmental situations which led to their development.

The low blood pressure of adrenalectomized animals can be raised by the injection of desoxycorticosterone.⁵⁰ This substance controls the distribution of sodium and potassium, and secondarily, the volume and viscosity of the blood and the mechanical power of muscle including the heart. Whether these factors are the sole means by which the adrenal cortex controls the blood pressure is uncertain but in adrenal insufficiency the renin mechanism for blood pressure control is also abnormal.

A loss of renin substrate is found in adrenal insufficiency.⁵¹ In animals with adrenal insufficiency administration of desoxycorticosterone restored the plasma substrate and blood pressure,⁵² the vascular aspect of the mineral and fluid disturbance being counteracted by this endocrine mechanism. Whether salt shortage can evoke the activity of this adrenal mechanism, including the renin substrate changes, is a question which has not yet been answered by experiment. Here again, as in the case of the post-pituitary mechanisms, we are uncertain as to the true correlation of the various related functions such as sodium excretion, potassium mobilization, loss of tissue potassium, hemoconcentration and blood pressure.

The alarm reaction described by Selye⁵³ and others may well be the key to the part played by the adrenocortical mechanisms in cardiovascular regulation. In brief, Selye's observations show that violent

trauma and other stimuli producing shock, result in immediate cellular changes in the adrenal and lymphatic systems and in the production of edema. Teleologically speaking, shocking injuries are the prime occasions for increased formation of tissue fluid and at the same time necessitate the mobilization of the maximum blood volume. That the lymphatic system and the adrenal cortex with its salt regulating and protein regulating effects should play a part in the defense against such traumata is only to be expected. To date, our knowledge of this mechanism is somewhat deficient with respect to the involvement of physiological and biochemical phenomena but the edema discussed in Selye's report suggests that in these circumstances the reabsorption of tissue fluid is unable to keep up with its emergency production.

Though evidence is still incomplete we can discern four general situations which are met by four overlapping humoral mechanisms. These are shock and hypotensive emergencies met by renin, water shortage met by vasopressin, physical danger or violent somatic activity by epinephrine, and stress on salt metabolism by adrenocortical hormone.

The emergency of special effort, and epinephrine's part in the adjustment to it, are closely defined. It can be anticipated that with added knowledge, the nature of the other three situations will be defined more accurately than I have here been able to define them. Quite possibly other situations, each with its adjunct hormone, will emerge.

THE ROLE OF THE INVOLUNTARY NERVOUS SYSTEM

Attention has been unduly focused on the details of cardiovascular reflexes since there is no broad generalization to form a framework for their interpretation. The cardiovascular proprioceptive reflexes, organized in the medulla, are concerned with insuring the compatibility of simultaneously occurring cardiovascular events and thus averting the breakdown of the cardiovascular system itself.

These medullary cardiovascular reactions are not usually directed to the coördination between cardiovascular activities and the interests, activities, and safety of the organism as a whole, except in so far as these latter are dependent on the maintenance of an adequate coronary, and perhaps cerebral circulation. For example, the Bainbridge or accelerator reflex coördinates the frequency of the heart beat with the rate of venous inflow thus insuring that the heart may adjust its work output in an orderly fashion both by beating more often and by expelling

more blood per beat. Closely allied medullary reflexes affect the heart's metabolism enabling it to liberate more energy, and that more efficiently, in circumstances where it does more work. At the same time Anrep's coronary dilating reflex assures the heart of a blood supply adequate to meet an increased demand.

In somewhat similar fashion the moderator reflexes from the aortic arch and carotid sinuses seem designed, in part at least, to guard the pressure and diastolic time available for the coronary flow when a rising blood pressure or systolic output is throwing a big load on the heart. At the same time these vasosensory zones guard the internal carotid blood supply and thus protect the cardiovascular system against the fatal disaster of medullary ischemia and perhaps cerebral compression.

THE ROLE OF THE HIGHER NERVOUS SYSTEM

The self-regulatory mechanism consisting of the heart, great blood vessels, and medulla is controlled by nerve impulses coming down to it from higher levels of the brain. The full analysis of this control is complex and incomplete but it seems to be in the hypothalamus that the combined nervous and endocrine integration orders the relations between the cardiovascular system and the sometimes conflicting interests which it serves. Here also seems to lie the integration of the metabolic, emotional, intellectual and exteroceptive factors which make varying demands on the cardiovascular system.

Unsatisfactory coördination at this level may well be responsible for the complex psychosomatic syndromes arising when anxiety states cause a dominance of one organ system's activities over that of others.

In a few cases, apparently, fairly well integrated voluntary control can be exerted through these various levels to different parts of the cardiovascular system. Thus reports have been published of voluntary cardiac arrest,⁵⁴ of voluntary pulse acceleration,⁵⁵ and local vasoconstriction and vasodilatation.

Enough has been said to indicate the possibility that by thinking along the lines of the analysis suggested it may be possible to reduce a large amount of miscellaneous cardiovascular information to a simple and more comprehensible form.

SUMMARY

An analysis of available knowledge of cardiovascular physiology

suggests that this information may be reduced to a simple and comprehensible form which may be summarized as follows:

The cardiovascular system like other body systems has such a physical and chemical make-up that the proper performance of its function is largely inherent. The activity of each tissue provides the chemical means of increasing its own blood supply.

The cardiovascular activities (and other activities, too) of many parts of the body are integrated and coördinated by the endocrine mechanisms to meet certain classes of emergency.

The heart, medulla, and cardio-medullary reflexes constitute a unit to maintain the integrity of the blood supply drained from the aorta in response to metabolite production and endocrine activity.

The higher parts of the brain provide rapid initiating adjustments whereby the cardiovascular system may be adjusted to new situations of exteroceptive, intellectual or emotional origin.

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THE EXCRETION OF STRONG ELECTROLYTES*†

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OUR knowledge of the mechanism of the tubular reabsorption of electrolytes has until recently been practically nil. The problem has seemed to present many complications. That there would be mutual interference in the reabsorption of electrolytes was anticipated, first, from the necessity of maintaining osmotic equality between the proximal tubular urine and the plasma, and second, because the essential feature of electrolyte control has seemed to be the maintenance of total base, which in turn is distributed in some specified manner between the two chief anions, chloride and bicarbonate. Furthermore, the data on chloride and bicarbonate reabsorption in the frog, *Necturus*,¹ rat and guinea pig² obtained by micropuncture studies, revealed that the reabsorption of chloride was certainly, and that of bicarbonate was probably distributed between the proximal and distal tubules, and there was *a priori* reason to suspect that these proximal and distal processes were fundamentally different in nature and subject to different types of control. Hence the task of describing electrolyte excretion quantitatively does not promise to be a simple one.

An effective start in this problem has, however, been made by Pitts and Lotspeich³ in their study of the excretion of bicarbonate. Examination of the relations between the plasma bicarbonate concentration and bicarbonate excretion in the dog shows that the renal threshold for excretion is approximately 25 mM. per liter; below this level, essentially all the filtered bicarbonate is reabsorbed; above this level, the rate of excretion is roughly a linear function of the plasma concentration. This would be the result if the renal tubules reabsorbed filtered water and bicarbonate in the proportions of 25 mM. per liter, and rejected all

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filtered bicarbonate in excess of this. Since the quantity of water excreted from the glomerular filtrate is relatively small, as a first approximation it would be expected that "bicarbonate reabsorption per liter of glomerular filtrate" would remain fixed at the value of 25 mM. at all levels of bicarbonate above the threshold. Pitts and Lotspeich present data purporting to demonstrate this constancy in various animals under various experimental conditions.

Accepting for the moment the constancy of the above relationship, it must be noted that the mathematical operation of factoring data on any aspect of renal function by the filtration rate has three implications. First, it tends to eliminate simultaneous errors in the two terms attributable to errors in the timing or collection of urine samples. Second, it tends to eliminate differences, as between different individuals, in renal size, since in general various aspects of renal function in different animals show a rough correlation with the filtration rate, a correlation attributable to morphologic balance between glomerular and tubular function. Such a correlation between filtration rate and the maximal rate of reabsorption of glucose (glucose Tm) is not so evident in the dog because of marked changes in filtration rate associated with the dietary regime,⁴ but the correlation is evident in man,⁵ and a high degree of correlation between filtration rate and the maximal rate of tubular excretion of diodrast⁶ and p-aminohippuric acid⁷ has been clearly demonstrated in man. Assuming that a high degree of correlation exists between the filtration rate and the tubular capacity to reabsorb bicarbonate, attributable only to morphologic balance, then factoring bicarbonate reabsorption by filtration rate will tend to reduce the differences between different animals. There is, however, a third and more important implication in this factoring operation, namely, that bicarbonate reabsorption may be *functionally* related to the filtration rate in any one animal. This can only be established by showing that reabsorption increases or decreases with filtration rate in a single animal where, we may presume, the morphologic contribution of the tubules will remain constant despite variation in filtration rate. Pitts and Lotspeich's data seem to establish that this is actually the case with bicarbonate, since as the filtration rate increases in any one dog the rate of reabsorption of bicarbonate increases in a proportional manner. Glucose Tm in the dog and man, and sulfate⁸ and phosphate⁹ Tm in the dog are apparently determined by absolute limitations in the tubular transport mechanism.

and are not influenced in any one individual by variations in the filtration rate. A situation where the rate of reabsorption is functionally related to the filtration rate in all physiological ranges requires a new interpretation.

In explaining this phenomenon, Pitts and Lotspeich start from the premise that roughly 80 per cent of the water of the glomerular filtrate is reabsorbed in the proximal tubule, regardless of the absolute filtration rate. They posit that the concentration of bicarbonate in this reabsorbate is *limited to a value of not more than 25 mM. per liter*. Secondly, they posit that in the distal system bicarbonate reabsorption is limited to a maximal rate of 0.5 mM. per minute, a figure based on a dog of such size as to have a filtration rate of 100 cc. but one which is independent of the actual filtration rate. In the Pitts-Lotspeich hypothesis we thus have two tubular maxima, a *concentration maximum* in the proximal reabsorbate, this reabsorbate amounting in volume to 80 per cent of the glomerular filtrate, and an absolute maximum in the distal system which is independent of the filtration rate.*

Pitts and Lotspeich suppose that when the plasma level of bicarbonate is 25 mM. per liter or less, 80 per cent of the filtered bicarbonate is reabsorbed in the proximal reabsorbate while the 20 per cent which is passed to the distal tubule is reabsorbed in the process of acidifying the urine. On elevation of the plasma bicarbonate above 25 mM. per liter, all bicarbonate in excess of this concentration is rejected in the proximal tubule and this moiety, together with that 20 per cent which normally is not reabsorbed, is passed to the distal system where quantities from zero up to 0.5 mM., depending on the activity of the acidifying mechanism, will be reabsorbed. Any excess over the sum of proximal reabsorption plus distal reabsorption will be excreted in the urine. Frank excretion of bicarbonate will begin when the total reabsorption amounts to approximately 25 mM. per liter of glomerular filtrate formed, and hence the system will operate to maintain the plasma level at 25 mM. per liter. Since proximal reabsorption is four times as great as distal reabsorption, total reabsorption will vary in rough proportion to the filtration rate no matter what the concentration-reabsorption relation in the distal process may be.

The hypothesis advanced by Pitts and Lotspeich, that a fluid of

* Distal reabsorption is related to the acidification of the urine, a process which has been explored in an exemplary manner by Pitts and Alexander,¹⁰ but one which need not concern us here. The proximal reabsorptive process, on the other hand, is isohydric in that bicarbonate is reabsorbed as such without change in the H⁺ ion concentration of the tubular urine.

constant composition in respect to bicarbonate is reabsorbed in the proximal tubule, is an ingenious one, but it presents a serious philosophic difficulty. The authors carefully record the qualification that, "How the concentration of bicarbonate in the proximal reabsorbate is limited to 2.5 millimols per 100 cc. (of reabsorbate) is beyond our present comprehension." Were it necessary, which it is not, this qualification would relieve them of any criticism in what is said below. They do, however, note as a matter of history that the reabsorption of a fluid of constant composition with respect to bicarbonate recalls Cushny's concept that the tubular reabsorbate has an optimal composition in respect to many constituents (resembling Locke's solution). It is perhaps unfair to criticize Cushny's choice of words in speaking of the reabsorption of a *fluid* of optimal composition since quantitative concepts had not developed in Cushny's time to a point where one could ask for specific details as to how such an operation might be carried out. We must, however, ask the question now.

How can the tubules reabsorb a fluid of constant (or maximal) composition with respect to bicarbonate? Do the tubule cells reach out with a Maxwellian hand and scoop in a microscopic droplet of tubular urine containing exactly 25 mM. of sodium bicarbonate per liter, squeezing out the excess bicarbonate between its Maxwellian fingers before returning this ideal fluid to the plasma? Not only must the excess bicarbonate be squeezed out, but also all the urea, creatinine, inulin, etc. not reabsorbed by the renal tubules, all chloride, phosphate, sulfate, glucose, creatine, etc., in excess of reabsorption, and all the substances which are excreted by the renal tubules and not reabsorbed—these substances must be excluded or included with quantitative precision if all the requirements of tubular reabsorption and excretion are to be met. It would seem that the reabsorption of a *fluid* of specified composition with respect to bicarbonate, or with respect to any other solute, is a deceptive verbal trap. We need not look for Maxwellian fingers to count the number of bicarbonate ions per unit volume of water (i.e., the *concentration per se*) either in the tubular urine or in the tubule cell, but it would seem to require Maxwellian ingenuity to separate bicarbonate ions simultaneously with the requisite number of water molecules from all other species admixt therewith in the tubular urine, without either picking out bicarbonate ions and water molecules *individually*, or by absorbing tubular urine *en masse* and then re-excreting

all the undesirable constituents. To quote a criticism of Cushny's ideal fluid theory written ten years ago: "It is open to question if the hypothesis of the tubular reabsorption of a fluid of optimal composition is really a simplification. In order that the tubules may reabsorb a fluid of optimal composition containing a large number of chemical substances in different concentration, there would seemingly be required just as elaborate physical-chemical apparatus as for them to reabsorb each of these constituents separately and independently."¹¹ So we return to the alternative interpretation, that what the tubules really do is to absorb bicarbonate ions and water molecules *separately* and *independently*, though perhaps in such proportions that the net result is as though they reabsorbed a solution of constant composition with respect to these constituents.

Is it conceivable that the proximal tubule can reabsorb water molecules "separately and independently," without reference to anything else? The distal tubule apparently does this when it abstracts water molecules from a mixture of sodium chloride, urea, creatinine, and other solutes, and, by reducing the water content of the residual urine, raises its osmotic pressure to several times that of the blood. So long as it is permissible to suppose that the distal tubule actively reabsorbs water molecules *per se* in making a hypertonic urine, we cannot dismiss the possibility in the proximal tubule.

We are, however, not forced to believe that the proximal reabsorption of water is necessarily an active and independent process: it may be a wholly passive one. As sodium (with its attendant chloride and bicarbonate) is reabsorbed the osmotic pressure of the tubular urine tends to be reduced and, if the proximal tubule is significantly permeable to water, water may simply diffuse back into the plasma to maintain the osmotic U/P ratio close to unity. In this view, a liter of water would be passively reabsorbed for each 145 mM. of sodium reabsorbed, and the net effect would to all appearances be the reabsorption of a fluid of constant composition. This sequence would follow the reabsorption of glucose, amino acids, phosphate and all other constituents of the tubular urine—in each case the precise osmotic equivalent of water would follow the reabsorbed solute back into the blood, without specific intervention on the part of the tubule. For simplicity, the passive reabsorption of water in the proximal tubule presents a very attractive hypothesis.

If the proximal reabsorption of water is a matter of passive diffusion, one might expect the proximal tubular urine to be at times at least slightly hypotonic to the blood. Walker, Bott, Oliver and MacDowell² obtained a hypotonic urine from the proximal tubule of the rat in only two out of twenty-one instances, but their observations were made on unilaterally nephrectomized animals which were generally loaded with sucrose or saline, both of which circumstances may have increased the filtration rate per nephron and altered the conditions of proximal reabsorption. Or perhaps in the normal animal the movement of water is so rapid that osmotic equilibration is almost instantaneous. In any case, the available data do not exclude the passive diffusion hypothesis.

Lotspeich, Swan and Pitts¹² have presented a limited examination of chloride excretion in the dog. As in the case of bicarbonate, the quantity of chloride reabsorbed is directly proportional to the filtration rate, not only in different animals but in the same animal, at the rate of 115 mM. per liter.*

Additional evidence of this functional relationship can be derived from data in the literature. The reabsorption of chloride in dogs receiving various saline infusions has been described by Hare, Hare and Phillips.¹³ These authors did not examine their results from the present point of view, but recalculation of their data shows that in any one dog the chloride reabsorbed per unit of glomerular filtrate is remarkably constant, regardless of marked changes in filtration rate resulting from the administration of saline, and despite the administration of large doses of antidiuretic hormone. The mean rate of reabsorption in the intact of Hare, Hare and Phillips is 111 mM. per liter, as compared with 115 mM. per liter in the data presented by Lotspeich, Swan and Pitts on acidotic dogs. Barclay and Cooke¹⁴ have recognized the above relationship in the data of Hare *et al.*, but offer no interpretations in terms of renal mechanism.

Mokotoff, Ross and Leiter¹⁵ have similarly found that in normal subjects and subjects in heart failure (in some of the latter the filtration rate is extremely low) the quantity of sodium reabsorbed varies directly as the filtration rate, reabsorption being in the proportion of 133 mM. for each liter of filtrate formed. This relationship is also evident in the data of Talbott, Pecora, Melville and Consolazio¹⁶ on sodium reabsorption in patients with Addison's disease and pan-hypopituitarism.

In looking at the over-all aspects of sodium (or chloride) reabsorption, too much emphasis must not be placed on the high degree of correlation between the quantity reabsorbed and the filtration rate. A gross linear relationship inevitably issues by definition if the urinary excretion of sodium is small: the equation appropriate to the excretion of any substance which is completely filterable but subsequently reabsorbed by the tubules (neglecting the Donnan equilibrium) is

$$(1) \text{PC}_t = T + UV$$

* The reabsorption of chloride must be conditioned by the reabsorption of bicarbonate, and vice versa, since these anions are extensively interchangeable in the plasma, and, as demonstrated by Pitts and Lotspeich, elevation of plasma chloride decreases the reabsorption of bicarbonate and vice versa. It is not known how the reabsorption of one anion conditions the reabsorption of the other.

where P is the plasma concentration in mg. per cc., C_f the filtration rate in cc. per minute, T is the quantity reabsorbed and UV the quantity excreted, both in mg. per minute. Dividing by C_f ,

$$(2) P = T/C_f + UV/C_f$$

If UV is zero or negligibly small, T will vary directly as C_f , the slope of the curve T vs. C_f (or the ratio of the two terms) being equal to P . It so happens that UV seldom exceeds 20 per cent of T and is generally less, while P is nearly constant in all individuals; hence when T is plotted against C_f it has a high linear correlation, with only small deviations attributable to variations in P and UV .

Thus the above correlation only expresses the fact that sodium (or chloride) and water will be reabsorbed in some constant proportion as a formal consequence of equation (2) so long as the absolute quantities of both substances excreted are but small fractions of the quantities filtered. What is required is to discover the determinants which govern the small deviations from this formal relationship when P or C_f are varied independently.

Stimulated by the Pitts-Lotspeich hypothesis for bicarbonate reabsorption, we have examined¹⁷ the reabsorption of sodium and water in the dog, first, in respect to whether these processes are intrinsically dependent or whether sodium can be reabsorbed independently of water; and second, as to whether the urine formed in the proximal system is or is not invariably isotonic with the plasma, i.e., whether water is reabsorbed in the quantity required by the passive diffusion hypothesis.

Osmotic diuresis was induced by infusion of 25 per cent mannitol solution at approximately 0.8 cc. per kg. per minute in trained, unanesthetized dogs. The filtration rate was measured by the creatinine clearance and sodium, chloride, bicarbonate and mannitol were determined in plasma and urine by standard methods.

When the concentration of mannitol in the plasma (and hence in the glomerular filtrate) is raised to substantial levels the mannitol retards by its osmotic pressure the reabsorption of water in the proximal system, and increasing quantities of water are delivered to the distal system, exceeding the reabsorptive capacity of the latter and resulting in marked increases in urine flow (osmotic diuresis). Under such conditions a large fraction of the water of the glomerular filtrate may be

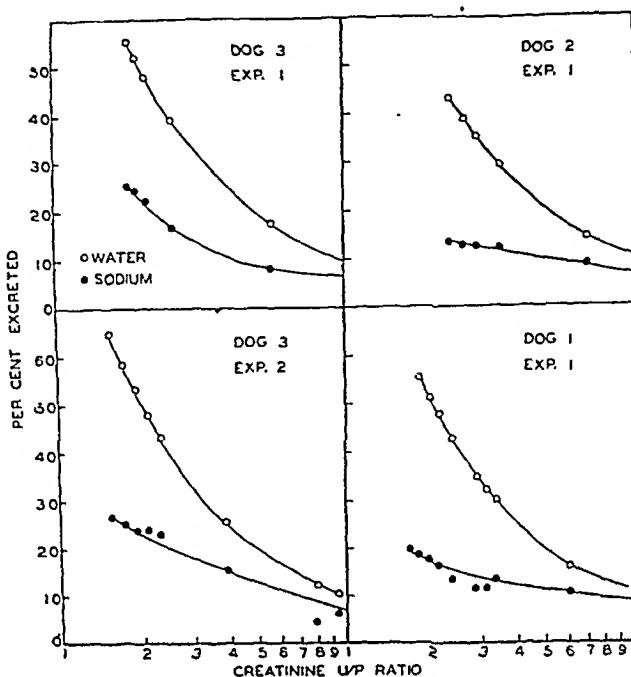


Fig. 1. The relative fraction of filtered sodium and water excreted in the urine during progressive osmotic diuresis induced in the dog by the intravenous administration of mannitol. The sequence of urine collection periods begins at the right and moves progressively to the lower creatinine U/P ratios as the diuresis increases in magnitude.

The mannitol sweeps much more water than sodium into the urine, indicating that sodium reabsorption is an active process which is only slightly disturbed by the conditions of the experiment.

excreted in the urine and the creatinine U/P ratio may be reduced to low values.¹⁸

Four such experiments are shown in Figure 1. It will be seen that it is possible to sweep out as much as 65 per cent of the filtered water while sweeping out only 13 to 27 per cent of the filtered sodium. A fifth experiment, not illustrated here, gave similar results.* The data will not be recorded here, but in these experiments chloride followed sodium, as might be expected. Bicarbonate excretion remained small even at large urine flows. These experiments demonstrate that the reabsorption of sodium is operationally independent of the reabsorption of

* It has been shown that during sulfate diuresis in the rabbit, a relatively small fraction of the filtered chloride is excreted despite the excretion of a considerable fraction of the filtered water.

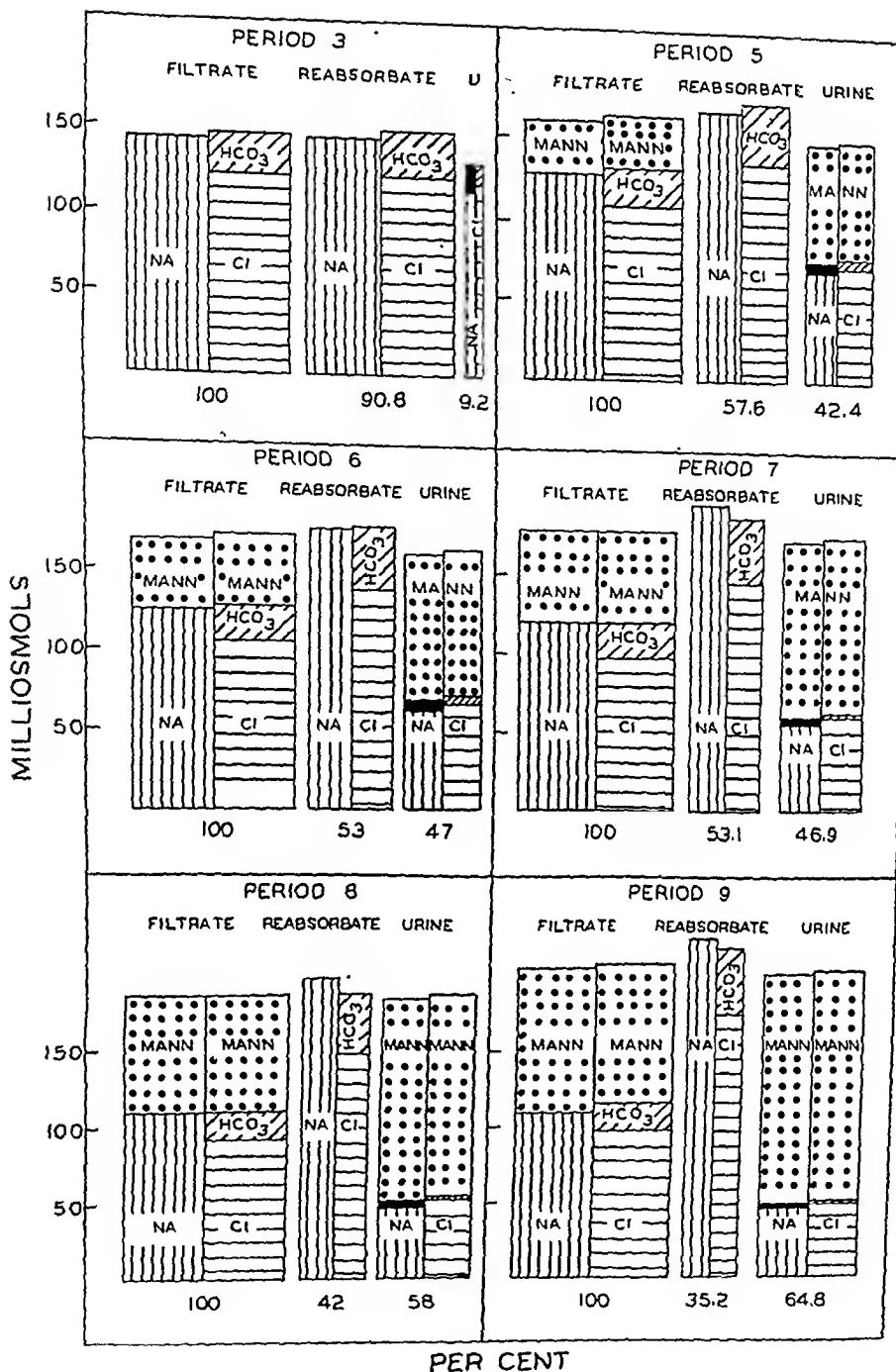


Fig. 2. Six urine collection periods from an experiment in which progressively increasing osmotic diuresis was induced in a dog by mannitol. The osmotic constituents of the filtrate (left) urine (right) and the total reabsorbate (center) as calculated by difference, are plotted in terms of milliosmols. (K is shown in solid black). The figures below the blocks show the relative volumes of filtrate, reabsorbate and urine formed per minute, the volume of filtrate in each instance being taken as 100.

As the plasma concentration of mannitol rises, this substance contributes an increasing fraction to the osmotic pressure of the plasma and urine. The three fluids remain, however, essentially isotonic, indicating that the fluid delivered to the distal tubule is itself isotonic with the plasma.

water, and that any interpretation involving the reabsorption of an "ideal fluid" or one of "optimal" composition must be abandoned.

Calculations based upon the above experiments also demonstrate, we believe, that the proximal reabsorbate is in general isotonic with the plasma. Evidence has been presented that under normal conditions some 85 per cent of the filtered sodium and water are reabsorbed proximally;²¹ although the final composition of the urine is specifically determined by the operations of the distal tubule, the net operation of the latter upon the fate of the glomerular filtrate as a whole is small. Under conditions of substantial osmotic diuresis, the quantity of proximal urine delivered to the distal tubule is so great that the specific operations of the latter, normally small in absolute magnitude, are swamped in the flood, so to speak, and the composition of the urine must come to reflect closely the composition of the fluid delivered to the distal tubule by the proximal system.

Figure 2 shows the detailed data on six urine collection periods in an experiment with mannitol diuresis. This experiment is one of five which have given the same results. In the experiment illustrated a 25 per cent solution of mannitol was infused at the rate of 1.1 cc. per kg. per minute. The plasma mannitol concentration rose from zero in period 3 to 3070 mg. per cent in period 9, the urine flow increasing from 4.6 to 31.5 cc. per minute and the creatinine U/P ratio falling from 11.5 to 1.62. When we add up the osmotic constituents of the plasma, on the one hand, and of the urine, on the other,* we find that within the limits of experimental error the osmotic pressure of the urine remains equal to that of the plasma, despite the fact that in the latter part of the experiment mannitol supplies a large fraction of the osmotic pressure of both fluids. Since the urine is simply what is left over after the abstraction of the reabsorbate, it follows that the reabsorbate itself has throughout the experiment remained isosmotic with this plasma. This evidence merely confirms, in a sense, the observations of Walker, Bott, Oliver and MacDowell² in the rat and guinea pig, but the observations of these investigators were of necessity confined to the first half of the proximal tubule; our present data extend the principle of isosmotic reabsorption to the over-all proximal operations in the kidney.

* No figure has been made for the reabsorption up to 10 per cent of mannitol, as recently suggested by Bott, Parker and Earle.²²

² We use the terms isosmotic reabsorption and reabsorbate only to indicate the over-all operation of the proximal tubule, and we emphasize that the reabsorption of sodium and water occur simultaneously at any point in the proximal tubule.

of the dog, and under much more drastic conditions than obtained in the experiments of the Long Island investigators.

We are then in a position to say that although the proximal reabsorption of sodium and water are operationally independent processes, they proceed in such a manner that the proximal urine (and hence the proximal reabsorbate) remains in general closely isosmotic with the plasma.*² This is consonant with the view, suggested above, that the reabsorption of sodium is an active process and that water passively diffuses back through the proximal tubule and thin limb under the resulting osmotic gradient.^{†‡}

This view affords an attractive explanation of the function of the thin segment of the loop of Henle. The older idea, that because this segment occurs only in the Classes (birds and mammals) where ADH promotes water reabsorption, it is the locus of the formation of a concentrated urine and of osmotic work, has never had strong appeal because its flat epithelium does not, by contrast with the distal tubule, seem cytologically constituted for such a function. Our present interpretation would be identical with that of Shannon,²³ who some years ago proposed that the thin limb serves to promote osmotic equilibration by passive diffusion of water between tubular urine and plasma after the bulk of the sodium, etc., has been reabsorbed proximally.[§] We would interpret the coincidence of the evolution of the thin limb and of the activity of ADH in promoting water reabsorption (which we refer to the distal tubule) as an adaptation facilitating reduction to a minimum of the water load delivered to the distal tubule where final water and sodium reabsorption must be effected. To deliver a variable excess of fluid to this terminal segment would conceivably be disadvantageous to its precise operations in the critical retention of sodium and water, especially where these two functions are themselves possibly sharply limited by critical constants.

The above conclusions lay the foundations for a more detailed ex-

* More correctly, of course, one should refer to the renal interstitial fluid rather than plasma, but for brevity we will consider the interstitial fluid as invariably isosmotic with the plasma.

† This statement should be qualified to the extent that conditions can be conceived where the proximal urine may be hypotonic to the plasma. Such conditions will be considered in a subsequent paper.

‡ We cannot positively exclude the possibility that active reabsorption of water may proceed independently of sodium reabsorption in such a manner as to maintain an isosmotic reabsorbate, but this interpretation requires that the active process be limited by an osmotic U/P ratio of 1.0, which as matters stand would leave us with no evidence for such an active process.

§ Shannon supposed, incorrectly we now believe, that all the sodium was reabsorbed in the proximal system and that a very dilute urine, equivalent to that obtained during water diuresis, was delivered to the distal tubule.

ploration of sodium and water reabsorption. Nominally, we are required to consider four processes, proximal sodium and water reabsorption, and distal sodium and water reabsorption. Since, under conditions of isosmotic reabsorption, the relative quantities of sodium and water in the proximal reabsorbate are contingent on the osmotic composition of the plasma, which is, of course, available to measurement, only one of the remaining terms must be determined in order to afford a quantitative description of both proximal and distal operations.

That some sodium is reabsorbed by the distal tubule is demonstrated in the frog and *Necturus* by the data on chloride of Walker, Hudson, Findley and Richards,¹ and there is at least an implication that this is the case in the data of Walker *et al.*² on the rat. These studies show that a significant reabsorption of water occurs below the proximal tubule, presumably in the distal tubule,* but the actual volume of water reabsorbed distally is unknown. Ever since the recognition of the functional difference between obligatory and facultative water reabsorption,²¹ the latter has been attributed to the distal tubule, which would mean that this segment normally receives about 15 per cent of the glomerular filtrate for reabsorption.

That the distal reabsorption of sodium and water are operationally independent of each other must be accepted so long as the distal tubule is accepted to be the locus of facultative water reabsorption. This facultative process may vary from some substantial value to zero, depending on the presence or absence of ADH; and this variation is not accompanied by a commensurate variation in sodium excretion. Indeed, there is no evidence that the latter is subject to analogous "facultative" control. (We do not overlook the possible significance of abrupt changes in the secretion of adrenocortical hormones).

We therefore accept that about one-eighth of the water of the glomerular filtrate is delivered to the distal tubule for facultative reabsorption. So long as the proximal fluid remains isosmotic with the plasma, it follows that an equal fraction of the filtered sodium also reaches the distal tubule where it is largely reabsorbed, since far less than this amount is customarily excreted. What is of chief interest to

* It would perhaps be consonant with all available facts to attribute facultative water reabsorption to the thin limb (it could be supposed that ADH promotes the passive diffusion of water in this segment, or even in the proximal tubule) but at least one circumstance argues against this interpretation. The fraction of the glomerular filtrate (*ca.* one-eighth) available for water diuresis is relatively independent of the absolute value of the filtration rate;²⁴ this constancy seems difficult to explain if the water of water diuresis represents a residue which has simply failed to diffuse back in the proximal system in the absence of ADH.

us at the moment is the upper limits of distal reabsorption of water and sodium.

It has been noted that systems involving tubular transport have with few exceptions been demonstrated to be limited by maximal rates—or at least by rates which do not change beyond the limits of experimental error with increasing load once the load has exceeded some critical value. In general these "maximal rates" of tubular transport are at least roughly reproducible in any one animal under basal conditions. Whether these liminal phenomena issue from limitations in available energy or limitations in the enzymatic transfer system need not concern us now. Distal reabsorption of water, unlike proximal reabsorption, appears to be an active process comparable with other active tubular transport systems, and as such it might be anticipated *a priori* that the absolute quantity of water per unit time would also have some upper, limiting value in cc. per minute. We may designate this supposed maximal rate as $T^d_{\text{MH}_2\text{O}}$, using T_m in the general sense of a limiting value in any tubular transport system and T^d to indicate specific reference to the distal tubule. $T^d_{\text{MH}_2\text{O}}$ may be substantially larger than the load of water normally delivered to the distal tubule. Similarly we may designate the maximal rate of sodium reabsorption in the distal tubule as T^d_{mNa} , emphasizing that neither of these supposed constants has as yet received adequate experimental verification. $T^d_{\text{MH}_2\text{O}}$ and T^d_{mNa} would of course only be reached if the distal load of water or sodium, respectively, were equal to or exceeded the maximal reabsorptive capacity for either substance, and $T^d_{\text{MH}_2\text{O}}$ would be reached only if the reabsorptive process were maximally activated by ADH. At partial states of ADH activation distal water reabsorption ($T^d_{\text{H}_2\text{O}}$) would be less than $T^d_{\text{MH}_2\text{O}}$, and, in the absence of ADH, might decrease to zero.

The experimental demonstration of these suppositious constants is obviously complicated by such variables as the absolute magnitude of the filtration rate from moment to moment, the variable endogenous secretion of ADH, and, at least during oliguria, by the maximal osmotic pressure of the urine,* as well as by a possible velocity effect which, during osmotic diuresis, may operate against osmotic equilibration in the proximal system.

* The lower limit of urine flow when the distal load is less than $T^d_{\text{MH}_2\text{O}}$ is doubtless determined by the osmotic ceiling against which the distal tubule can concentrate the urine.

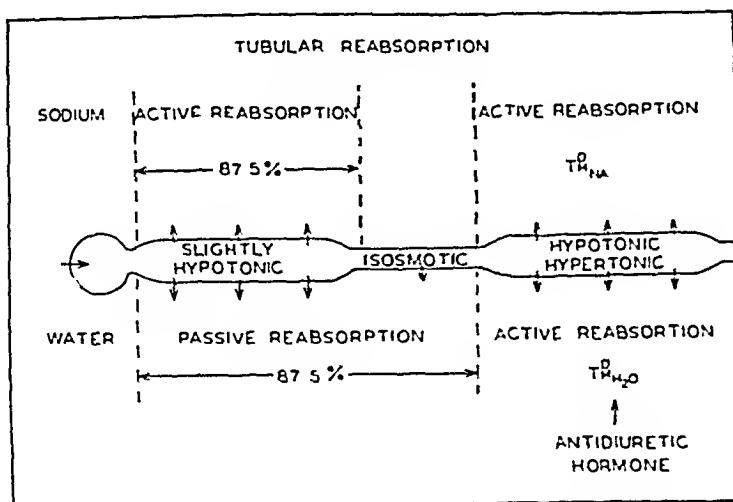


Fig. 3. In the hypothesis presented in this paper it is presumed that sodium with chloride and bicarbonate is reabsorbed in the proximal tubule by an active process, leading to the formation of a slightly hypotonic urine. In consequence of this hypotonicity water diffuses back into the plasma so that a fluid essentially isotonic with plasma is delivered to the distal tubule. It is conceived that the function of the thin limb is to promote osmotic equilibration. Reabsorption in the proximal tubule and thin limb accounts for roughly seven-eighths of the glomerular filtrate, leaving one-eighth to be operated upon in the distal tubule.

It is believed that water and sodium are actively but independently reabsorbed in the distal tubule by processes which are limited by maximal rates ($T^d_{H_2O}$ and T^d_{Na}). The distal reabsorption of water is activated by the antidiuretic hormone which, with the osmoreceptors of the supraopticohypophyseal system, comprises the mechanism for the control of water equilibrium.

We have for some time been engaged in the intensive investigation of this problem, but we have been unable as yet to demonstrate the stability of these constants under a variety of conditions, possibly because of the above complicating factors, and possibly because our hypothesis is oversimplified.** However, we believe the hypothesis will be useful in guiding experimental work and in visualizing over-all renal function in the maintenance of salt and water balance (See Figure 3).

Since $T^d_{H_2O}$ can vary from zero to T^d_{Na} in consequence of variations in ADH secretion, water equilibrium will be maintained

** We have evidence of an hysteresis-like phenomenon, whereby maximal water and sodium reabsorption increase gradually during the course of several hours following a sudden increase in filtration rate, despite a constant filtered load. This may reflect variable endocrine activity induced by sodium administration or adaptive changes in the tubules themselves.

despite marked variations in the filtration rate, except under conditions of osmotic diuresis when the water load exceeds T^d_{MHO} or distal reabsorption is opposed by the diuretic agent. This is equivalent to saying that at all times the sodium concentration of the plasma will be regulated to a critical value through the supraopticohypophyseal system by the retention or rejection of water.

So long as the fraction of filtered sodium reabsorbed proximally remains approximately constant, or does not vary through too wide a range, the load of sodium delivered to the distal tubule will increase or decrease with the filtration rate. At some critical filtration rate this load will be exactly equal to T^d_{MNA} and the subject will be exactly in sodium equilibrium. If the filtration rate is increased the distal load will be increased and come to exceed T^d_{MNA} , leading to the excretion of the excess sodium. Where sodium is excreted more rapidly than water, the sodium content of the plasma will decrease and this reduction of osmotic pressure, acting through the supraopticohypophyseal system, will lead to the distal rejection of water until the critical osmotic pressure of the plasma is restored.

Conversely, if the filtration rate is reduced, the distal load of sodium will be less than T^d_{MNA} and sodium reabsorption will be essentially complete. Where sodium reabsorption exceeds water reabsorption, the ultimate increase in the osmotic pressure of the plasma, operating through the supraopticohypophyseal system, will increase the distal reabsorption of water until the critical osmotic pressure of the plasma is restored.

At a given plasma concentration of sodium there will be one and only one filtration rate at which the subject will remain exactly in sodium equilibrium. It will be convenient to refer to this filtration rate as the equilibrium filtration rate.

Fluctuations in the filtration rate above or below the equilibrium filtration rate may be of considerable importance in sodium balance. It is common knowledge that the oral administration of moderate doses of isotonic saline (ex. one liter in a man) does not result in an abrupt excretion of fluid, as does the administration of an equal volume of water. The saline is excreted slowly and may not be recovered for a number of hours. On absorption of the saline no change occurs in the osmotic pressure of the plasma and one wonders why the saline is excreted. It has recently been recognized that one method of increasing

the filtration rate consistently in the dog, and this is possibly true in man, is the administration of saline. The increase in filtration rate after the rapid intravenous administration of saline occurs more slowly and outlasts by a considerable period the sojourn of the saline in the vascular tree, as indicated by dilution of the plasma proteins or reduction in hematocrit.²⁵ It appears probable that the increase in filtration rate increases the load of sodium to the distal tubule until this exceeds T^d_{mnA} , when the excess sodium is excreted. Plasma dilution results and, through the supraopticohypophyseal system, the excess water is ultimately excreted. The slowness with which glomerular activity is adjusted may explain the slowness with which saline diuresis is initiated, and the relatively small increase in the filtration rate at the peak of diuresis may be responsible for the relatively slight magnitude of the diuresis.

Conversely, after the withdrawal of plasma (isotonic fluid) from the body, its restoration is effected in a relatively short time. Extreme hemorrhage and shock²⁶⁻³⁰ are accompanied by a marked reduction in filtration rate and it is quite possible that a reduction of small but significant magnitude may occur after moderate blood loss. A similar cycle of events might operate to conserve salt and water under conditions of excessive sweating, vomiting, diarrhea, etc.

It will be noted that in all these operations only very small changes in filtration rate need be involved. In a man with a plasma sodium concentration of 138 mM. per liter and a filtration rate of 130 cc. per minute, a decrease or increase of filtration rate of only some 6 cc. per minute would be required to retain or excrete 15 gm. of sodium per day, if proximal reabsorption continues to account for 80 per cent of the filtered sodium. Variations of this order are scarcely beyond the experimental error of our present methods of clinical investigation. Moreover, nearly all our available data are based upon short period observations, whereas in the maintenance of sodium equilibrium, we are of course concerned with glomerular activity as distributed over the entire 24 hour period, and it is highly probable that this activity is influenced by meals, posture, exercise, sleep and possibly many other factors.

By coupling together the renal mechanism controlling the excretion of sodium, the supraopticohypophyseal mechanism for controlling the excretion of water, and the glomerular apparatus controlling the filtra-

tion rate, we would have an integrated system that will not only regulate the composition of the extracellular fluid, but its volume as well. The above considerations lead us to inquire whether there exists in the body a mechanism by which expansion or contraction of the extracellular fluid compartment tends automatically to increase or decrease the filtration rate. The existence of such a mechanism seems highly probable, but we know nothing about it at the present time, nor do we have any certain knowledge of how, within the glomerular apparatus itself, changes in filtration rate are effected.* We are certain that these changes cannot be accounted for solely on the basis of plasma dilution. A most important field lies open here for investigation. Further progress in this problem requires an adaptation of the clearance technique to studies extending over a period of 24 hours or longer, whereby some of these factors may be studied.

A single clinical application of the above hypothesis will be useful. Seymour, Pritchard, Longley and Hayman,³¹ and more recently Merrill³² have reported that the renal blood flow and filtration rate are reduced in chronic congestive heart failure, the latter to one-half or one-third of the normal. Merrill attributes the continued, complete reabsorption of sodium to the reduction in the amount of sodium filtered in consequence of the reduced filtration rate, an interpretation which is in accord with our hypothesis. When the filtered load of sodium is reduced, the load delivered to the distal tubule is less than T^d_{mna} and sodium reabsorption is essentially complete. Through the supraopticohypophyseal system water is retained in characteristic proportions to sodium, and isotonic edema fluid accumulates in the body. Interruption of this cycle requires the restoration of the filtration rate to normal, reduction of the sodium intake, or reduction in sodium reabsorption by a mercurial diuretic.

Mokotoff, Ross and Leiter¹⁵ have confirmed Merrill's observation that the filtration rate is reduced in cardiac failure, and demonstrated further that this reduction is not due to neurogenic vasoconstriction: in only one of 11 instances did the filtration rate increase during high

* A unique and interesting implication of the above considerations is that a 'steady state' cannot be achieved by the progressive, uniform excretion of excess sodium in accordance with renal clearance principles, since an infinite time would be required to reach equilibrium; it appears that this difficulty is resolved in this as in other physiological systems (the regulation of respiration, blood pressure, body temperature, etc.) by over-compensation and hence oscillation above and below the steady state as a mean. In its long-range operation the above system will cause the filtration rate to oscillate above and below the equilibrium value, and the plasma sodium concentration to oscillate above and below a mean value determined by the critical, osmotic threshold of the supraopticohypophyseal system, damping in respect to both sodium and water retention being effected by the critical renal barriers T_{mdna} and T_{mdito} .

spinal anesthesia in patients in whom the blood pressure was maintained with ephedrine.³³ Farnsworth³⁴ also reports low filtration rates in some patients in failure, but in others the data fall within the normal range. Merrill's suggestion conforms, as said above, with our present knowledge of renal function, but it remains to be determined that this is the only and necessary condition for salt and water retention. The general absence of edema in hypertension and frequent absence in chronic diffuse glomerulonephritis, where the filtration rate may be markedly reduced, seems to require either that nephrons are destroyed in a nearly unitary manner in these diseases, maintaining glomerular-tubular balance in the functional parenchyma, or that other factors may be operating in cardiac failure.

Merrill considers the reduced filtration rate in cardiac failure to be a concomitant of renal ischemia, the renal blood flow being reduced in favor of more vital parts of the circulation, as in hemorrhage and shock. He believes that the decreased renal blood flow is attributable to the secretion of renin, which he and his colleagues have demonstrated to be present in the renal venous blood during cardiac decompensation.³² Whatever the agent, it may be suspected that it reflects a disturbance of the mechanism, the existence of which is suggested above, whereby glomerular activity is adjusted to the volume of the extracellular fluid.

The studies of Brod³⁵ indicate that in normal subjects the filtration rate, as judged roughly by the clearance of endogenous creatinine-like chromogen, increases during the morning and decreases at night, particularly during sleep. It is well known^{36,37} that the urine flow and electrolyte excretion tend to follow this diurnal pattern, though the physiological basis is obscure. The change in urine flow is possibly related to a change in filtration rate or possibly to a diurnal pattern in ADH secretion. In some patients with congestive heart failure, the above pattern is reversed, and Brod has shown that the nocturia is associated with a marked increase in the endogenous creatinine chromogen clearance, indicating that it is related to an increase in filtration rate. Workers in this laboratory have noted that in subjects with essential hypertension, nocturia when present may be associated with a significant increase in endogenous creatinine clearance and chloride excretion, suggesting that the filtration rate is fluctuating close to the equilibrium level required for saturation of the distal tubule with respect to sodium. The cycle, although not consistently present, suggests some close rela-

tionship between sleep and control of the glomerular apparatus.

Future studies of electrolyte and water balance must take cognizance of such long-range changes, recognizing the principle that the kidneys, functionally poised in glomerular-tubular balance, the extracellular fluid, the vascular tree, and the heart, constitute a system the integration of which is essential not only to salt and water balance, but also to the efficiency of the circulation.

SUMMARY

Recent investigations have shown that the tubular reabsorption of electrolytes (bicarbonate, chloride and sodium) is functionally related to the filtration rate, presumably because an approximately constant fraction (\approx seven-eighths) of the filtered sodium and water are reabsorbed by the proximal tubule and thin limb, regardless of the filtration rate.

During osmotic diuresis induced by the intravenous infusion of hypertonic mannitol solution in the dog, the fraction of water reabsorbed proximally is substantially reduced and large quantities of fluid are delivered to the distal tubule. However, the fraction of sodium reabsorbed proximally is not reduced commensurately. Thus, as much as 65 per cent of the water of the glomerular filtrate may be excreted in the urine at a time when only 13 to 27 per cent of the filtered sodium is being excreted. On this basis it is believed the reabsorption of sodium by the renal tubules is operationally independent of the reabsorption of water.

Under these conditions the composition of the urine is believed to represent with close approximation the composition of the urine at the end of the thin limb. Since, during osmotic diuresis, the osmotic pressure of the urine closely approaches the osmotic pressure of the plasma, it follows that the proximal reabsorbate is itself isosmotic with the plasma. It is inferred that this isosmotic relationship obtains under ordinary conditions. This concept is consonant with the view that proximal reabsorption of sodium is an active process and that under the resulting osmotic gradient water passively diffuses back through the proximal tubule and thin limb to maintain an isosmotic relation.

The " facultative" reabsorption of water, representing about one-eighth of the water of the glomerular filtrate, is believed to be a function of the distal tubule. In view of the evidence that the urine delivered

from the proximal tubule is isosmotic with plasma, it follows that an additional fraction of sodium is reabsorbed distally. It is suggested that the distal reabsorption of sodium and water are independently limited by maximal rates of tubular transport, such as have been demonstrated in other tubular transport systems.

These concepts of electrolyte excretion are discussed in relation to the excretion of isotonic saline, the retention of sodium and water in hemorrhage, shock and related conditions of dehydration, to edema formation in cardiac failure, and to diurnal variations in the excretion of electrolytes and water.

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EDEMA OF HEART FAILURE*

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PROBLEMS related to the mechanism of cardiac edema have appealed to the clinician and physiologist alike because of the abundance of material available for study. The edema fluid is readily obtained by pricking the skin, and the techniques for studying the venous pressure and other aspects of the circulation have been highly developed.

Our original approach to the problem was the analysis of the protein content of the edema fluid.¹ Fluid obtained from the skin and subcutaneous tissues of patients with congestive failure contains little protein. This fact alone indicates that the primary mechanism of cardiac edema can be neither lymphatic obstruction nor increased capillary permeability. The finding is compatible, however, with hypoproteinemia, or increased venous pressure, or retention of fluid by the kidney.

Since the plasma protein concentration is normal in many patients, hypoproteinemia can be eliminated as the primary factor in cardiac edema. A moderate increase in venous pressure produces edema which contains relatively little protein. The same type of low-protein edema results from the administration of physiologic saline solution at a rate greater than the capacity of the kidneys to excrete fluid. Examination of the fluid alone did not distinguish between these mechanisms. This finding led to additional observations on the relationship between plasma volume and edema fluid. In chronic congestive failure, the plasma volume is elevated and the protein content of the edema fluid is low. In normal subjects the venous pressure in a large part of the body may be increased by motionless standing. This uniformly produces a fall in plasma volume, as fluid is forced through the capillaries by the high hydrostatic pressure. The decrease in volume may be corrected in part by drinking several liters of physiologic saline solution, but even with persistent drinking the plasma volume falls. As urine flow practically ceases, body weight increases. These observations suggested that

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the edema of congestive failure might not be due to an elevated systemic venous pressure because the edema of congestive failure is associated with an increased blood volume. Fluid given to a normal subject lying horizontal at a rate greater than can be excreted by the kidney causes a large blood volume and edema fluid low in protein. This combination is present in acute nephritis,² pregnancy, and congestive failure. These cumulative data suggest that the primary mechanism of cardiac edema is related to the fact that the fluid intake exceeds the fluid output, and that a disturbance in renal function produced by heart failure may be the primary cause of cardiac edema.

Because of the emphasis usually placed on the causative role of an elevated venous pressure in the edema of heart failure, the relationship between the venous pressure and cardiac edema was examined at greater length. It was obvious that in many subjects, edema persisted long after the venous pressure returned to normal and that in others edema returned without a corresponding rise in venous pressure. Observations on patients with superior mediastinal obstruction or patients with inferior caval ligation showed that a change in venous pressure of the magnitude seen in early congestive failure did not produce the massive edema so characteristic of heart failure. Warren and I examined the sequence of events in two patients who had been made edema-free by salt restriction and the administration of mercurial diuretics.³ Both patients formed edema on a high salt intake. The edema and an increase in plasma volume preceded any measurable rise in venous pressure, indicating that the elevated venous pressure was not the cause of retention of fluid but was, instead, secondary to it.

On rigid sodium restriction, patients with congestive failure tolerate water remarkably well, but the addition to the diet of a small amount of sodium will cause swelling. These data pointed to the primary retention of sodium with resultant retention of water. The role of chloride, also, appeared to be a secondary one, because the administration of NaHCO_3 caused edema while NH_4Cl did not.

The problem now resolved itself into a study of the mechanism by which sodium was retained when the heart failed. A study of the hemodynamics of the kidney in congestive failure seemed a logical step. A preliminary survey of the literature, however, was discouraging, and a few random studies in our laboratory demonstrated that though renal function was highly abnormal in certain patients with congestive fail-

ure, it was normal in others. After a time, we realized that these differences existed because the circulatory state of our patients varied. One group of patients will develop congestive failure during their usual activity, but will have adequate circulations at rest. Observations on such patients show normal resting cardiac outputs, normal renal blood flows, and normal responses to added salt in diet. These circulatory measurements may be normal in the presence of edema because it takes time to complete a diuresis. Obviously, the mechanism of edema formation at rest could not be studied in such patients whose resting circulation was adequate. In contrast, however, certain patients become edematous at rest whenever they are placed on a normal diet. They become edema-free only when the intake of sodium is sharply restricted or after the repeated administration of mercurial diuretics. This latter group who formed edema at rest was selected for the study of the mechanism of edema formation.

The data on cardiac output in patients selected on this basis are of interest.⁴ The basal cardiac output as related to the surface area of the body is nearly always lower than in normal subjects. As the oxygen consumption is within normal limits unless the subject is uncomfortable or dyspneic, this means that the arteriovenous oxygen difference is greater than normal. The marked disturbance of the pumping ability of the heart is magnified by light exercise. There are certain exceptions to the observation that failure is accompanied by an absolute lowering of the resting cardiac output. In patients who are restless and uncomfortable and in those with anemia or thyrotoxicosis, failure may occur in the presence of a cardiac output above the normal resting level. It should be noted that an elevated cardiac output is characteristic of patients with similar physiologic or pathologic disturbances who have no heart failure. It is not surprising, therefore, that when the circulation becomes inadequate they develop the signs of circulatory insufficiency before their outputs fall to the normal level. In summary, the observations on cardiac output indicate that the signs of congestive failure develop whenever the cardiac output is inadequate for the body needs over a prolonged period of time. The absolute value at which the cardiac output becomes inadequate will depend on the needs of the body for blood. In myxedema, the level will be low; in anemia and hyperthyroidism, high.

Merrill studied the renal blood flow and filtration rate in this group

of patients who formed edema at rest.⁵ He found the renal blood flow to be reduced to $\frac{1}{3}$ to $\frac{1}{5}$ of the normal value, and the filtration rate to be reduced to $\frac{1}{2}$ to $\frac{1}{3}$ of normal. The filtration fraction was increased. The renal arteriovenous oxygen difference was increased. The extraction of PAH by the kidney was normal.

The fall in filtration rate resulted in a marked reduction in the amount of sodium filtered. The tubules reabsorbed almost entirely the greatly reduced amount of sodium presented to them. Even so, in absolute terms, they reabsorbed much less sodium than normal subjects under similar conditions. It appears that one of the functions of the tubular cells is to reabsorb sodium, and that the cardiac patient has no mechanism to depress this function to a level which will allow the sodium to leave the kidney. Therapeutically, of course, we solve this difficulty by temporarily poisoning the cells with an organic mercurial preparation. It is true that many situations exist in which the filtration rate is lowered without the development of edema. In a patient with Addison's disease, the filtration rate is lowered and sodium is still excreted in spite of the falling blood level. In this instance, disturbances in tubular function because of adrenal insufficiency over-balance the decrease in filtration rate. In chronic glomerular nephritis, the filtration rate is lowered. If the tubular dysfunction is less severe than glomerular dysfunction, edema occurs; if tubular dysfunction is more severe, the patient develops a marked sodium deficiency on a low salt diet. If the tubular and glomerular lesions balance, neither edema nor dehydration develop. Cardiac failure is peculiar in that a profound disturbance in glomerular filtration occurs in the presence of a minimum of demonstrable tubular damage.

The high filtration fraction indicated that the reduction in renal blood flow was the primary cause of the reduced filtration rate. The question, then, resolved itself into an analysis of the factors reducing the renal blood flow. Merrill⁵ presented data to show that the reduction in filtration rate and renal blood flow was not correlated with changes in right atrial pressure, but was related to changes in cardiac output. Throughout this talk, the term "inadequate cardiac output" has been used. We are now in a position to define this term more precisely as it relates to cardiac edema. The absolute level of cardiac output is of little importance. It is inadequate whenever for a long period of time too little blood is pumped to give the kidneys their normal share. The kid-

neys suffer early and to a greater extent than other organs when the blood supply is reduced. The mechanism of the fall in renal blood flow in the presence of an inadequate cardiac output has not been determined. Merrill⁵ did demonstrate that the fall in renal blood flow was greater than the fall in output. A decreased renal blood flow occurs not only in chronic congestive failure, but in normal subjects on motionless standing or vigorous exercise and in patients in shock. It would be helpful if the exact time relationship were known. How long must the cardiac output be decreased before the renal blood flow falls? How long does it take the renal blood flow to rise after the cardiac output is increased?

Myers⁶ has recently shown that the hepatic blood flow is low in chronic congestive failure. However, in contrast to the findings in the renal circulation, the fall in hepatic flow is proportional to the fall in output. The difference in the response of the renal and hepatic blood flows to the same stimuli is well shown in anemic patients without failure. In this instance, the hepatic blood flow is greatly increased,⁷ while the renal flow is moderately reduced.⁸

While recent studies have emphasized the role of the kidney in cardiac edema, clinical observation has long demonstrated that many patients with heart failure have an elevated venous pressure. A rise in right atrial venous pressure may be accomplished in three ways: (1) increase in blood volume, (2) increase in vascular tone, and (3) shift of blood from the lesser to the greater circulation, or vice versa. In patients with chronic failure and a fixed low cardiac output, the venous pressure varies directly with blood volume.² In normal subjects, sympathico-mimetic drugs, such as paredrinol,⁹ cause a rise in venous pressure without a rise in cardiac output; and plethysmographic observations on these subjects demonstrate a rise in venous tone. Clinical observations suggest that any sharp reduction in cardiac output below the body needs results in a rise in vascular tone unless neurogenic collapse occurs, or tissue necrosis or infection is extensive.¹⁰ If the blood volume is reduced, as in hemorrhage, there is a rise in vascular tone without an elevation in venous pressure. If the blood volume is increased, or normal, as in heart failure, a rise in vascular tone is accompanied by a rise in venous pressure. The sudden fall in venous pressure which occurs after digitalization may be the result of a change in venous tone. Whether this is a direct effect of digitalis or secondary to the rise in

cardiac output has not been determined.

The shifts of blood from the lungs to the general circulation have not been studied in heart failure. As left ventricular failure is the common situation, usually blood from the peripheral circulation is accumulating in the lungs. If, however, the situation is reversed and right ventricular failure predominates, the blood available for backing up behind the right heart is that which is pumped by the right heart to the left heart plus the blood which can be delivered to the left heart by constriction of the pulmonary vascular tree. It is doubtful if enough blood is ever mobilized from the lungs by constriction to produce an appreciable rise in the systemic venous pressure unless venous constriction in the peripheral bed occurs at the same time.

Reichsman and Grant¹¹ have shown that certain patients with mitral stenosis and auricular fibrillation who are digitalized will have a rise in venous pressure if the digitalis is omitted. This fits in with our observations. Unfortunately, it does not help to solve the problem of edema because it is probable that in these patients the rise in venous pressure is coincident with a fall in cardiac output. We are then left with the fact that either variable, the reduction in cardiac output or the rise in venous pressure, might be responsible for initiating the chain of events leading to gross edema.

Changes in capillary pressure and in tissue pressure are extremely important in determining the deposition of the fluid retained by the kidneys. If physiologic saline solution is given to a subject who is leaning motionless against a wall, the fluid will accumulate in the lower part of the body because of the high capillary pressure. If he lies down, the fluid will have to be given at a much more rapid rate to exceed the rate of excretion by the kidneys. It will be more evenly distributed and will first become visible as puffiness about the eyes. In the loose periorbital tissue, a large amount of fluid may accumulate without an increase in tissue pressure.

The effect of a rise in venous pressure on the distribution of salt and water may be illustrated by a patient whose inferior vena cava had been ligated for recurrent pulmonary emboli. The brachial venous pressure was 60 mm. of water, and the femoral, 200 mm. On a low salt diet, there was no pitting edema. On a high salt diet, the patient gained weight and developed pitting edema of the lower half of the body. Similarly, patients with low grade venous obstruction may have very

little edema until the onset of congestive failure. Then massive edema of the obstructed part may occur before considerable edema is demonstrable elsewhere.

It is at once obvious that patients with heart failure differ from normal subjects in the way they handle fluid when the intake exceeds the output. The patient with failure tends to store a large amount of fluid in the lungs, and massive pulmonary edema may precede any detectable signs of peripheral edema. In congestive failure, the pulmonary arterial pressure is elevated.¹² If a portion of this rise in resistance is a reflection of high left atrial and pulmonary capillary pressures, we have a satisfactory answer for the predisposition to pulmonary edema in the patient with failure. While this assumption is supported by indirect evidence, direct measurement of the pulmonary venous pressure has not been made.

Use of mercurial diuretics and rigid restriction of sodium in the diet has modified our conception of cardiac decompensation. The symptoms of congestive heart failure can be divided into two large groups. The first group includes symptoms referable to poor function of tissues and organs caused by the inability of the heart to maintain the blood supply of the part. The muscular weakness of congestive failure falls into this class. The second group of symptoms is related to the accumulation of excess salt and water in the organs and tissues of the body. Dyspnea, orthopnea, and cough belong here. These symptoms which result from edema will disappear on rigid salt restriction even though the circulation has not improved. The dyspneic, orthopneic, miserable patient becomes a comfortable, normal-appearing ambulatory subject as long as sodium is withheld. The extent of symptomatic improvement in such a patient would lead one to say the heart was now compensated. Actually, the circulation may not have improved, and return to a normal diet may produce a recurrence of symptoms.

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BULLETIN OF
THE NEW YORK ACADEMY
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VENOUS THROMBOSIS AND
PULMONARY EMBOLISM *

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INTEREST has become more universal in the problem of venous thrombosis and pulmonary embolism in the past decade than appears to have been evident in any previous era. Although there is still much to be learned about this common complication of illness, injury, parturition and surgery, we believe some progress has been made. In spite of the various established aids in the prevention of thrombosis and in the treatment of the disease in its non-fatal form, the fact remains that a considerable number of people still die from this cause. The literature is voluminous concerning the good results obtained by the treatment of patients who develop thrombosis of the leg veins and sublethal embolic processes. Few reports have been made however that parallel the incidence of quickly fatal massive pulmonary embolism occurring in the same institution during the period of time covered by the study. Obser-

* Given March 5, 1948 before the Section on Surgery of The New York Academy of Medicine.

vations on the preventive methods tried are also open to criticism since one can, by comparison with a previous or control group of patients, obtain only an estimate of the values rather than the accurate determinations often possible in the study of other problems. Since the above statements apply to our own publications on the subject, as well as those of others, it is obvious that we do not have the final solution. We believe, however, if all interested in this field will continue to view the situation in a critical manner, that better and probably simpler methods of management will be evolved.

We are aware that in a group of patients of the same sex, age, physical condition, afflicted with the same disease and treated in the same manner, there will be only a certain percentage who will develop thrombosis of the leg veins with or without pulmonary involvement. It seems that there should be evolved simple criteria to indicate which patients would be likely to have such complications. It is true that in determining the prothrombin level in a large number of patients, we find a few with a slightly lowered and a few with a slightly elevated prothrombin time. On the whole, however, the present methods of measurement would fail to give us sufficient evidence to warrant extra precautions in most cases. Since at this time we have no reliable laboratory studies to help us predict the outcome in the majority of patients, we must use the clinical data pertaining to the subject that is available. Gradually there is being collected clinical material that will in time make it possible to estimate the risk of thrombosis and embolism in given pathologic states for various age and sex groups. It is quite probable that the risk will prove to be lower in certain geographical locations than in others. It is known that thrombosis occurs less frequently during the summer months than during the winter in New England.

Cardiac patients as well as those with other medical diseases requiring quiet, sedation, bed rest in a sitting position, etc., are common victims of thrombosis and embolism.

Extensive malignancy, involving the abdominal viscera particularly, tends to lead to these complications even in the inoperable phase. It is not unusual to have fatal embolism occur during the otherwise normal convalescence following operative procedures on malignancy of the colon and stomach.

Acute intra-abdominal infections, such as appendiceal abscess, are more prone to be associated with thrombosis and embolism than infec-

tions elsewhere. Since acute small bowel obstruction gives a high incidence of this syndrome, it may well be that ileus or abdominal distension is more important in contributing to these complications than the infectious process itself. It has appeared obvious that depleted patients from any cause whatever are more subject to thrombosis than are those in good general condition.

Furthermore, we believe that much can be accomplished in lowering the incidence of thrombosis and embolism by utilization of the many pre- and postoperative general measures now commonly known. Elimination of stasis in the leg veins by bandage and posture, muscular activity in bed and early walking are all helpful and generally practiced.

Certain definite facts concerning the development of thrombosis are now well established.¹ These are beginning to be recognized generally, but series of cases treated either prophylactically or therapeutically without consideration of these known predisposing factors are still being reported. The age of the patient is probably the one important factor most commonly ignored. Although it is possible to show that age in years can be used as a general rule, it remains for consideration that some patients of less than 50 years of age may be more deteriorated than others of 70. Actually, it appears that infirmity with its influence on muscular activity plays an important role. *Trauma involving the lower extremities* is likewise a well-known predisposing factor to thromboses of the veins. This may be comparatively minor in character such as a contusion or abrasion. Burns involving the lower limbs are likewise conducive to this complication. The frequent development of thrombosis following thigh amputations and fractures of the leg and hip region is now accepted.

In viewing this subject as a whole, it is obvious that we have two distinct methods of attack. These are treatment of the condition after evidence of its existence is apparent, or specific prophylactic measures that may prevent thrombosis. Aside from the general measures practiced in all patients that can be adapted to them, we have other means at our disposal to diminish the chance of thrombosis. It must be admitted that we cannot utilize many of the aids available in every case. Although prevention of stasis in the leg veins by posture, compression bandages and active or passive exercises can be carried out in a very high percentage of ill or postoperative patients, there are many instances when this cannot be effectively done. We also feel that under given circum-

stances, one form of specific prevention may be more suitable than another.

Our experience now covers a period of 20 years of awareness of the seriousness of the problem. The first decade was devoted to general measures of prevention of thrombosis and it appears that by these means, postoperative fatal emboli were reduced from 3 in 1000 to 1 in 800 cases in our clinic.² It must be remembered that during this time there was a gradual improvement in the preoperative preparation, operative technique and postoperative care. These measures reduced the operative mortality from other complications as well as those from thromboembolic disease. Slowly at first but with greater impetus during the past decade, attention has been directed to specific methods of prevention and treatment of this syndrome. As the operative mortality from other complications became reduced to such a low point, the sudden exodus from massive embolism became more impressive.

Perhaps enough has been said about the two types of thrombosis of the veins. It seems now that these should be thoroughly understood and accepted. Whether there is a common origin of the thrombus regardless of its type is somewhat irrelevant except from an academic standpoint. It seems doubtful to us that all thromboses are alike in the beginning. The sudden occurrence of pain and swelling in the leg associated with the elevation of temperature and pulse so characteristic of thrombophlebitis defines this form in a distinctive fashion. That a non-inflammatory thrombus should always precede it seems unlikely. In phlebothrombosis, we rarely have adequate evidence of the process until it is well advanced or until a pulmonary infarct has occurred. The legs on examination appear normal in the early stage and there is no noticeable reaction as manifested by a rise in temperature, pulse, and respiration on the clinical chart until an infarct, although often painless, has taken place. It is from this type of bland thrombosis that nearly all of the fatal emboli occur. The lack of inflammatory reaction in the vein is responsible for the clot remaining unattached to the vein wall. If all of the thromboses were immediately inflammatory in type, there would be only rare embolic deaths and these would come from a propagating thrombus at a higher level in the venous system. We have observed all gradations of the disease and it is certain that non-fatal phlebothrombosis will often develop into thrombophlebitis. This may be a gradual process actually requiring weeks of time on occasion.

Frequently, the swelling and pain in the leg characteristic of thrombophlebitis may not appear until long after the first infarct and rarely after femoral vein interruption for phlebothrombosis has been carried out. True phlegmasia alba dolens is now an unusual picture and is seen only in our clinic in patients treated elsewhere for some period of time before coming to us. The prolonged morbidity associated with this disease, so common 10 years ago, is no longer observed. Treatment of the condition in its early stages, whether it is inflammatory or bland in type, has eliminated the prolonged convalescence and sequelae seen in former years.

Up to January 1, 1948, over 2600 patients at the Massachusetts General Hospital have received some form of specific measures for the prevention of or the treatment of the thrombo-embolic syndrome. In this group of cases, there were 12 deaths related to the process toward which the treatment was directed. One can only estimate the number of fatalities in this group of patients if no specific treatment for the complication present or feared had been given. Deaths from pulmonary embolism occur in untreated cases in this hospital still, in spite of our alertness to the possibilities. In some instances, the type of illness or the condition or physical development of the patient seemed to offer a reasonable contraindication to any of the specific remedies available. Others occur in patients under the care of skeptics on the staff regarding the efficacy of the measures usually accepted. There occurred also rare instances of fatal embolism in patients that would ordinarily not be expected to develop such a complication. It seems fair by comparison of past and present experience to assume that the estimated deaths in the treated group would have increased tenfold had specific treatment been withheld. The following statistical analysis of our experience has been useful to us and may be helpful to others in the evaluation of this problem.

PROPHYLACTIC MEASURES

Although our earlier experience was confined to the general prophylactic measures mentioned above and so universally adopted, it will be assumed that such were carried out when feasible in all cases referred to in this presentation regardless of any specific methods used. Prevention of thrombosis, particularly in the veins of the lower extremities by any means whatsoever, is far more important than the treatment of

the condition after it arises. For this reason, we would like to discuss this phase of the question first. Since we have no reliable laboratory data to furnish us with a clue regarding the likelihood of thrombosis in the majority of patients, we must rely on clinical observations. In earlier publications, we have shown that fatal embolism is unusual under the age of thirty. Although rare instances occur, it would seem impractical at the moment to use any of the specific measures to prevent thrombosis that are now known to us. Also, it must be borne in mind that if thrombosis develops in younger patients, the warning signs are much more prone to be sublethal in character than in the aged. For this reason, we believe it is justifiable with few exceptions to use only general measures on patients under the age of 30 and treat to the best of our present ability the complications that arise.

In the middle aged group, we have a large percentage of patients who have no contraindication to the anticoagulants and can in large part be protected from thrombosis by their proper use. It is our feeling that the hazards of this form of treatment have not been sufficiently stressed. It is difficult to put down a simple, easily understood plan that can be utilized by most doctors or by a large percentage of hospitals. The best results have been reported by groups of physicians who have been able to concentrate on the problem without interference. They have had a good working knowledge of the problem as a whole and have had adequate laboratory facilities at their disposal. It is obvious that these drugs cannot be used empirically and that each patient must have complete, careful, and intelligent supervision. It is our feeling that patients in the older age group should more cautiously be given anticoagulants. Our reason for this opinion is based on a rather high percentage of deaths observed in our hospital when heparin or dicumarol was used in patients with arteriosclerosis. The percentages of cerebral hemorrhages in these patients has been too high to warrant its frequent use. Much of this experience was obtained in earlier years than those covered by this report and apply to the use of heparin in the treatment of bacterial endocarditis by the medical service.³

We feel that we have unquestionably established the safety and feasibility of interruption of the normal superficial femoral veins in the prophylaxis against thrombosis and embolism. This has not been generally accepted because physicians, who have not had such a procedure done on themselves or on their patients, cannot believe that interrupting

TABLE I—SUMMARY—THROMBO-EMBOLIC DISEASE

Massachusetts General Hospital—1937-1947

	No. of Patients	Fatalities
Prophylactic Dicumarol	536	2
Prophylactic Sup. Fem. vein interruption	871	4
Therapeutic Phlebotomy, Thrombectomy, and Fem. vein interruption	1260	6
Total	2667	12(0.45%)

a large vein in the thigh could be devoid of danger to that extremity. We were skeptical about it ourselves at first but came to realize, after adopting routine bilateral superficial femoral vein interruption in the treatment of thrombosis, that sequelae were negligible on the unthrombosed side. For these reasons, we feel that under proper circumstances and in suitable cases, this procedure is preferable to any other. This is particularly evident in patients who have injuries to the lower extremities where immobilization is necessary or where wounds prevent freedom of muscular activity. Likewise in the depleted, very ill patient with advanced carcinoma or infection and often on the basis of age alone, active exercises cannot be effectively carried out. Even if it were considered safe to use anticoagulant therapy in many of these patients, the duration of the treatment with its constant laboratory control would create a more serious hospital problem than prophylactic superficial femoral vein interruption.

It was possible to demonstrate in a controlled study of two similar groups of patients, of middle age treated by small doses of dicumarol postoperatively, that this drug was effective in reducing the incidence of thrombosis by 80 per cent. We feel that with a more intelligent use of this drug or a substitution of heparin in resistant patients that a further reduction would have been made. We are convinced, however, that indiscriminate use of anticoagulants without laboratory control will lead to fatal complications. One must weigh these possibilities carefully when these potent drugs are used. In both of our fatalities (Table I), following its use, justifiable criticism is obvious.

One patient aged 46 was known to have moderate hypertension. He had a simple partial colectomy with primary anastomosis for a constricting carcinoma of the sigmoid; 200 mg. of dicumarol was given on the first postoperative day and 14 hours later he had a large subarachnoid hemorrhage. The prothrombin time was 20 seconds over a normal of 19 seconds. Massive doses of vitamin K were given with a drop to normal in prothrombin time. Sixteen days later, however, his prothrombin time was 27 over a normal of 18 seconds. Since he continued to bleed intermittently, a carotid artery ligation was recommended and carried out by the neurosurgical service. The patient failed to survive this procedure. It is fair to say that this patient should not have had anticoagulant therapy. Furthermore, it seems doubtful that the 200 mg. dose of dicumarol with its usual delayed action could have influenced the original cerebral hemorrhage within 14 hours after its administration. The slight change in the prothrombin level 24 hours after giving the dicumarol may be within the limits of laboratory error.

The other fatality occurred in an 82 year old man who had a transurethral resection of his prostate. Eight days later, he developed an incarcerated sliding hernia and was operated upon 2 days afterwards. Following this, he received 200 mg. of dicumarol, by error, and 3 days later, 13 days after his prostatic resection, bilateral superficial femoral vein interruption was done as a prophylactic measure. The next day his prothrombin time was 26 over a normal of 18 seconds. The following day, now 15 days after the prostatic procedure, 5 days after herniorrhaphy and dicumarol therapy, and 2 days after femoral vein interruption, he bled massively from the prostatic bed. In spite of vitamin K and blood transfusions, his prothrombin time was not reduced to below 22 seconds. He bled twice more in the next two weeks and his N.P.N. reached 80 mg. per cent. Forty-six days after his initial operation, he had a sudden episode resembling cerebral hemorrhage and succumbed. Unfortunately, no autopsy was obtained. In this case, dicumarol should not have been used and we think that this is the oldest patient to have received this drug in our hospital. It appears that this patient may have been particularly sensitive to the drug.

It is important to observe that no patient receiving dicumarol therapy as a prophylactic measure died of pulmonary embolism. Since the two deaths reported above may well have been due to other causes than the dicumarol therapy, we feel that this drug when properly used

TABLE II

RESPONSE TO 200 MGM. PROPHYLACTIC DICUMAROL
1947—254 Cases

	<i>Good</i>	<i>Poor</i>	<i>Undetermined</i>	<i>Total</i>
Single Dose . . .	78	21	20	119
Multiple Dose . . .	113	20	2	135
Total . . .	191 (75%)	41	22	254

has much to commend it. We have observed another patient with almost fatal bleeding from misuse of dicumarol given elsewhere. This patient of 38 had undergone hysterectomy and had developed thrombophlebitis on the 11th postoperative day. Without laboratory control, the patient was given daily doses of dicumarol totaling 3500 mgs. in a three week period. Her thrombophlebitis had subsided and she was sent home. She was admitted to our hospital within twenty-four hours, bleeding from the nose, kidneys, and into the spinal fluid, and with a hemiplegia thought to be due to hemorrhage. After very heroic treatment with Vitamin K, and whole blood transfusions, her prothrombin time, which on admission was unobtainable because of lack of all clotting ability, was reduced to normal in 48 hours. She was well save for the residual paralysis from the cerebral hemorrhage on discharge 28 days later.

Table II shows the type of response to 200 mg. doses of dicumarol given prophylactically in 254 patients treated in the year 1947. Seventy-eight of these were given only 1 dose, while 113 had multiple doses. It appears that at least 75 per cent of these patients responded satisfactorily to this method of treatment.

Table III reveals the complications we have encountered with the drug, including the patients who developed phlebitis or infarcts in spite of its use. It appears that, even in those patients who show what we consider to be an adequate response to the drug, a few develop phlebitis and infarcts requiring femoral vein interruption. It is quite possible that these patients could have been more vigorously treated. We have increased the initial dose in certain very large individuals and have more

TABLE III

COMPLICATIONS OF PROPHYLACTIC DICUMAROL IN 496 PATIENTS
 Massachusetts General Hospital—1945-1947

	With Response	Without Response	? Response	Total
*Minor Bleeding	12	0	0	12
*Major Bleeding	1	0	0	1
**Phlebitis	2	5	4	11
**Infarct	—	6	5	11
Fatal Pulmonary Embolus	0	0	0	0
Deaths from delayed hemorrhage	1	1	0	2

* Requiring Vitamin K or Transfusion.

** Requiring Femoral Vein Interruption.

recently given subsequent doses when the prothrombin time has not indicated a suitable response.

Bleeding from suture lines and the tendency of large dead spaces to fill with blood after the use of dicumarol is to be noted. The typical examples of these are more frequent and copious hemorrhage in primary intestinal anastomosis, and the development of large hematomata in the pelvis following combined abdomino-perineal resections of the rectum. One hematoma with subsequent abscess following hysterectomy is noteworthy since this complication has not been seen in many years prior to dicumarol therapy.

Prophylactic superficial femoral vein interruption has been done on 871 patients between 1943 and 1947 inclusive. Table IV illustrates the gradual adoption of this procedure from 15 patients in 1943 to 317 in 1947. The prophylactic use of this method now represents 58 per cent of all femoral vein interruptions done in our hospital. This brings out the confidence we have gained in this type of protection. Since we have a definite increase in the age of the patient and severity of lesion in recent years it is evident that now a higher percentage than formerly of those treated on the Surgical Service can be logically protected from thrombosis and embolism by this method. It does, to some extent, involve medical patients also since the ratio of fatal embolism

TABLE IV

INCIDENCE OF THERAPEUTIC AND PROPHYLACTIC FEMORAL
VEIN INTERRUPTION IN 2,131 CASES

Massachusetts General Hospital—1937 to January 1948

	<i>Therapeutic</i>	<i>Prophylactic</i>	<i>Total</i>
1937-1942	202	0	202
1943	150	15	165
1944	208	72	280
1945	214	178	392
1946	259	289	548
1947	227	317	544
Total	1,260	871	2,131

is about the same as the number of beds available for medical and surgical cases.

In 4 of these patients treated by prophylactic femoral vein interruption, fatal embolism occurred. In 3 of these there was no past or present evidence that thrombosis was already established before femoral vein interruption was undertaken. The embolism in one of these may have originated in the proximal segment of the superficial femoral vein left in situ. Definite extension into the profunda femoris was found in one and this we believe led to the large propagating thrombus in the iliacs of sufficient magnitude to cause death. We feel that the dangers of interruption of the common femoral is greater than that of fatal embolism originating in the profunda femoris. Also it seems clear to us that the superficial femoral should be interrupted as close to the profunda femoris as is technically possible.

The other death in this group is definitely questionable from the prophylactic viewpoint. The surgeon felt in retrospect that thrombosis was present in the iliac veins at the time of interruption but was overlooked. This patient had been in the hospital twelve weeks under treatment for arteriosclerotic obliterative disease. The prophylactic interruption was done at the time of low thigh amputation. He died suddenly the day of operation and had, at autopsy, massive emboli of both pul-

TABLE V

EMBOLIC DEATHS SUBSEQUENT TO FEM. VEIN INTERRUPTION
PROPHYLACTIC

<i>Age</i>	<i>Sex</i>	<i>Disease</i>	<i>Operation</i>	<i>Interval between vein inter. and death</i>
67	M	Ca Sigmoid with Obstruction	Cecostomy, later Resection	16 days
54	F	Ca Stomach	Total Gastrectomy	34 days
63	F	Ventral Hernia	Repair	15 days
78	M	Arteriosclerotic gangrene	'Thigh Amputation—12 wks. after admission	8 hours

monary arteries, that appeared to have originated in the iliac veins. The pathologist's impression was that the thrombi were older than the number of hours elapsed between operation and death. However, since it was done on the prophylactic basis by one of our pioneers in this field we think we are justified in including it in the failures of the method (Table V).

It would not be possible to determine accurately the net salvage in this group of 871 patients. We have, however, made an accurate comparison between these and a similar number of patients unprotected by prophylactic femoral vein interruption. We have considered the sex, age, disease, type of operation, and service in the hospital in this comparative study. As seen in Table VI it appears that 37 of these patients might have died of pulmonary embolism if this preventive method had not been carried out. It must be pointed out, however, that other factors may have played a role and we are fully aware of the lack of scientific data desirable in such a report.

THERAPEUTIC MEASURES

Most workers in this field have stressed the routine general measures for the prevention of thrombosis and embolism mentioned earlier in this report. Also we, as others, interested ourselves in specific methods of treatment in nonfatal cases of embolism and thrombophlebitis.

TABLE VI

COMPARATIVE INCIDENCE OF POSTOPERATIVE THROMBOSIS
AND EMBOLISM

Age group 65 years or over—January 1, 1948

	Number of cases in each group	With Prophylactic Vein Interruption		Without Prophylactic Vein Interruption	
		Phlebitis	Fatal Embolus	Phlebitis	Fatal Embolus
Fractures Hip Region	130	3	0	23	10*
Leg Amputation	92	1	1	6	8
Colon Operations	111	5	1	16	6
Gastric Operations	94	7	1	9	4
Resection of Rectum	52	2	0	11	2
Genito-Urinary Surgery	50	4	0	3	2
Biliary Surgery	74	2	0	8	1
Pelvic Surgery	46	0	0	4	1
Hernioplasty	41	2	1	3	1
S.B. Obstruction	21	3	0	2	1
Neuro Surgery	7	0	0	0	1
Appendectomy	24	1	0	2	0
Heart Disease	23	0	0	4	0
Radical Mastectomy	20	0	0	1	0
Pancreatic Surgery	15	2	0	4	0
Esophagectomy	12	0	0	2	0
Miscellaneous	59	3	0	4	0
Total	871	35	4	102	37

* Because of medico-legal jurisdiction autopsy was not possible in all deaths following hip fractures.

Intravenous heparin was our first specific remedy and this drug, valuable as it is, proved in our early experience to be unsatisfactory. It was cumbersome to use and costly to the patient. Also we found it unreliable since one fatal embolism occurred during its use and another 48 hours after the patient appeared to be well following fourteen days of therapy. With Homans' influence so near us it was natural that we began to have confidence in phlebotomy, thrombectomy and femoral vein inter-

ruption. Gradually this method of treatment took precedent over all others although many cases were treated by anticoagulants, and procaine sympathetic blocks as well.

That anticoagulant therapy is effective in the hands of many workers is obvious from the numerous reports on the subject. The Scandinavian surgeons have made outstanding contributions to this field.^{4, 5, 6} Among the American physicians and surgeons using anticoagulants with satisfaction should be mentioned Murray and Best of Toronto,⁷ Allen of Rochester, Minnesota,⁸ and Evans and Dee of Boston.⁹ The latter deserve great credit for paralleling 57 sudden fatal emboli occurring during the time of their study. All of us have been amiss in not reporting these sudden embolic deaths that come with little or no warning. We are in the process of tabulating these cases in our own institution. Until these are carefully studied it will not be possible to determine the exact value of prophylaxis or treatment in this syndrome. From a purely pathologic viewpoint the number of fatal emboli in relation to the number of autopsies appears to be unchanged. It is obvious that many factors must be taken into consideration. Patients rarely die now of shock, peritonitis or pneumonia and the average age of surgical patients has increased. Also, the magnitude of surgical procedures is greater. Many patients who formerly died of other causes now live long enough to develop thrombosis and embolism.

Since our data on phlebotomy, thrombectomy and femoral vein interruption is available we will discuss this method of treatment further. Up to January 1st, 1948, 1,260 patients have been so treated in our clinic. The indications are given in Table VII. This shows that there has been a decreasing tendency to await nonfatal infarct from 41 per cent in 1942 to 14 per cent in 1947. Definite signs of thrombosis on examination of the legs has declined from 59 per cent in 1942 to 24.6 per cent in 1947. Recently a small percentage of patients have been subjected to superficial femoral vein interruption on the basis of the clinical chart only. We have observed that when there is a concomitant rise in temperature, pulse and respiration in an otherwise normal course of events we can be reasonably sure that thrombosis is present and infarct has occurred. In many of our massive embolic cases we could find this warning sign on the clinical chart in retrospect. These figures, as will be observed, are greatly influenced by our attitude regarding prophylactic femoral vein interruption.

TABLE VII
INDICATIONS FOR FEMORAL VEIN INTERRUPTION
Massachusetts General Hospital—1937-1947—2,131 Cases

	1937-42	1943	1944	1945	1946	1947
Chest pain as first symptom	41.0%	34.5%	32.5%	23.0%	16.4%	14.0%
Leg sign as first symptom	59.0%	56.3%	41.8%	33.7%	30.5%	24.6%
Positive clinical chart sign	0	0	0	0	0.4%	3.1%
Prophylactic Interruption	0	9.2%	25.7%	43.3%	52.7%	58.3%

TABLE VIII
EMBOLIC DEATHS SUBSEQUENT TO FEM. VEIN INTERRUPTION
THERAPEUTIC

Age	Sex	Disease	Operation	Interval between vein inter. and death
47	F	Intract. Facial pain	Lobotomy	23 days
71	F	Diabetic gangrene	Thigh amputa-tion	2 days
74	M	Ca Stomach Inoperable	Peritoneoscopy	38 days
66	M	Ca Stomach	Subtotal Gastrectomy	9 days
76	F	Cataracts	Enucleation	8 days
77	M	Phlebitis and Pulmonary Infarct	Medical patient	13 days

In this group of patients there were six who died as a result of further emboli. All of these patients had had nonlethal embolic processes prior to femoral vein interruption. The average age of this group was 69 years. Two had advanced cancer originating in the stomach, one was a diabetic with gangrene, one was hypertensive and had undergone bilateral cataract operations, one had had pre-frontal lobotomy for intractable facial pain and the other had had numerous previous attacks of phlebitis (Table VIII).

One can conjecture that many of the patients who survived would have died of embolism had nothing specific been done to prevent it. The net salvage is again impossible to determine. It must be borne in mind that these patients were saved the prolonged convalescence formerly seen in the treatment of thrombophlebitis. Post-phlebitic edema and ulcer does not occur in patients treated specifically in the early course of thrombophlebitis.

A small percentage of patients treated by phlebotomy, thrombectomy and femoral vein interruption had continued pulmonary infarcts. Occasionally these patients had pain and swelling and tenderness in the extremity where the thrombosis existed previously. These were treated by anticoagulants and lumbar sympathetic procaine blocks after vein interruption. Rarely it was necessary to ligate the inferior vena cava in patients who continued to have infarcts in spite of all these methods of treatment.

SUMMARY AND CONCLUSIONS

1. Up to January 1, 1948, over 2600 patients at the Massachusetts General Hospital have had specific efforts made to prevent or treat thrombosis and embolism. Some patients received a combination of methods accounting for the variation in total figures.
2. General prophylactic measures only were used in most patients under the age of 30. Specific treatment was indicated in a few of these because of the previous history of phlebitis or the type of lesion present. Therapeutic specific measures were carried out when indications of thrombosis or infarct occurred.
3. Four hundred and ninety-six patients between the ages of 40 and 65 were treated prophylactically by small doses of dicumarol post-operatively. None of these died of pulmonary embolism. The hemorrhagic dangers associated with the use of this drug are stressed. We believe that anticoagulants cannot be safely used empirically and that careful laboratory and clinical control is necessary.
4. Prophylactic bilateral superficial femoral vein interruption was done on 871 patients whose age, debility or disease indicated that a high percentage of them would be likely to develop thrombosis of the leg veins. Of these, four died subsequently of pulmonary embolism. This was a highly vulnerable group of patients and based on comparative experience there might have been expected 37 deaths from

embolism.

5. One thousand two hundred and sixty patients were treated by phlebotomy, thrombectomy and femoral vein interruptions after signs or symptoms indicated that thrombosis had occurred. Of these six died of further emboli. It is estimated that 60 of these might have succumbed if specific therapy had been withheld. In a small percentage of these patients anticoagulants and lumbar sympathetic procaine blocks were also used.

6. Deaths from sudden massive embolism still occur in our hospital. These are often without warning and in patients who have had no specific prophylactic measures instituted.

7. The diminished mortality from shock, infection and pneumonia in recent years results in thrombosis and embolism as a more prominent cause of death than formerly noted. Statistically a higher percentage of patients coming to autopsy now will reveal massive pulmonary embolism as the cause of death than was observed ten years previously.

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THE EARLY RECOGNITION OF POST-OPERATIVE VENOUS THROMBOSIS*

Increased Prothrombin Activity As An Aid To Diagnosis

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THE problem of venous thrombosis in the post-operative patient or in any patient who is confined to bed, has always been a challenge to the clinician and in spite of extensive laboratory and clinical study, it still presents many unanswered problems. The dramatic and often fatal complication of pulmonary embolism has justifiably received the greatest amount of attention, but the problem of the chronically swollen extremity and the post-phlebitic ulcer are equally perplexing. During the past decade, there have been rapid advances both in our understanding of the basic pathology and in methods of therapy, but the true etiology of the condition is unknown and there is no reliable means of predicting which individuals are liable to develop thrombosis and its complications. There is heated discussion between the advocates of proximal vein interruption and those who champion anticoagulant therapy, but if these two methods of therapy are to stand the test of time, there must be individualization of each patient and in many instances, one method should complement the other. There is great need for some laboratory or clinical method by which thrombosis can be predicted in the individual patient.

Our understanding of the manner in which venous thrombosis develops has been modified as a result of extensive investigation of the post-operative patient and of the conditions found at autopsy. The source of pulmonary emboli has been considered in the past to be almost entirely the thrombi formed about the site of an operation or in the small pelvic veins of the prostatic or ovarian plexuses. Small emboli

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undoubtedly do arise from these sources, but they are probably not the origin of large emboli or the massive fatal embolus. It is now believed that the veins of the leg are the more common source of emboli and that the most dangerous type of thrombus is that which develops in the small veins of the plantar aspect of the foot or in the calf and propagates proximally into the large veins of the legs without causing the typical signs of venous thrombosis. Homans¹ in 1934 suggested that bland thrombosis of the calf veins without inflammatory reaction was the source of multiple pulmonary emboli and was one of the first to perform proximal vein ligation. There is general agreement at present that the leg veins are the most common source of emboli. Denecke, and Olow² showed that the earliest symptoms are in the calf and plantar regions. Roessle³ in 1937 and Neumann⁴ in 1938 demonstrated in autopsy material that the calf and plantar veins are the common sites of thrombosis.

The modern concept of the pathogenesis of venous thrombosis differs from earlier opinions on the subject. In the past, femoral-iliac thrombophlebitis was considered to be the result of infection and thrombosis in the large veins of the thigh and groin with resultant venous obstruction, edema and the signs of phlegmasia alba dolens. This process probably occurs, but the clinical picture of the swollen, painful leg of thrombophlebitis more commonly develops as a result of thrombosis in the small veins of the calf or foot with propagation of the thrombus proximally until the entire femoral vein is occluded by a thrombus (Frykholm,⁵ Bauer⁶). In the earliest phase, a coagulation thrombus occurs in the small veins which may give no physical signs or symptoms. This may propagate proximally in the popliteal and superficial femoral vein without being attached to the wall of the vein so that the thrombus is actually waving in the blood stream and may at any time, break free as an embolus. This is the Bland Thrombosis of Homans^{7,8} or the Phlebothrombosis of Ochsner and DeBakey.⁹ If the process continues, the clot then becomes attached to the vein wall, the tributary veins become occluded by thrombi, and the typical signs of phlebitis become evident. This is probably the sequence of events in a vast majority of the patients with thrombo-embolism but it does not explain all situations. In post-partum sepsis the inflammatory process involves the pelvic veins and there may be extension of the thrombosis proximally to the iliac veins with massive embolism or via the ovarian veins with multiple

septic emboli. Pulmonary emboli in cardiac patients may have their origin from mural thrombi or from vegetations on diseased valves.

The etiology of venous thrombosis in an individual is usually difficult to evaluate but there are many factors which may be of importance, especially in the post-operative patient. The most obvious of these are physical factors which are present in varying degrees and which theoretically result in conditions favoring intravascular coagulation. Peripheral venous stasis, most marked in the lower extremities, is often present. Abdominal distension with compression of the abdominal veins causes stasis of venous blood in the legs and thighs. Decreased thoracic excursion as a result of pain from upper abdominal and thoracic incisions results in a decrease in the thoracic negative pressure which is so important in promoting venous return. Position in bed with the hips and knees flexed causes angulation of veins. Pressure on the veins of the legs and lack of muscular activity increase venous stasis. The dehydration which may occur after operations increases the viscosity of the blood and favors coagulation.

Post-operative infection plays a part in thrombosis and was present in 75 per cent of the cases of embolism reported by Morton and associates.¹⁰ The infection was not necessarily localized at the operative site but appeared to be a factor when involving any part of the body.

The age of the patient is an important consideration in venous thrombosis, and the majority of fatal pulmonary emboli occur in patients over 50 years of age. The condition of the heart is very important, as even in incipient cardiac failure there is peripheral venous congestion with stasis. The cardiac status also has an important bearing on the end results of pulmonary embolism. In patients who had no demonstrable cardiac disease, 41 per cent of pulmonary emboli were non-fatal; whereas, 92 per cent were fatal in patients with cardiac disease, and no patient survived a pulmonary embolus if cardiac decompensation was present.¹⁰ Another factor of importance in the older patient is the condition of the vessels. Atherosclerosis is usually considered to be primarily a disease of arteries, but the veins may also be involved.

When the venous circulation is impaired, the irregular intimal surface of an abnormal vein may act as the eddy point at which a thrombus develops. Peripheral vasospasm may contribute to slowing of the circulation and thrombus formation. Varicose veins with their sluggish flow are a particularly susceptible factor.

There are other factors directly related to the altered physiology of the blood during and after an operation. Waugh¹¹ has shown that there is decreased coagulation time in the post-operative period. He reported a "Heparin-Dilution" method of determining coagulation time which showed a definite decrease in time usually on the third and fourth post-operative days. We have obtained similar results in our laboratory using his method. Crafoord and Jorpes¹² have noted that a larger dose of heparin is rendered inactive in the blood during the first and second post-operative days than at other times and interpret this as indicating hyper-coagulability of the blood. There may also be some alteration in the platelets after operation. Wright¹³ believes that there is an increased adhesiveness of the platelets in the post-operative period with an accompanying rise in platelets. Tocantins¹⁴ has found a decrease in the number of platelets on the first, second and third days after an operation with an increase on the sixth and a maximum level on the tenth day. The increase is most marked after sepsis and splenectomy. Laffont and Sirjean¹⁵ found the platelet count elevated several days before puerperal phlebitis developed. Other changes in the blood such as an increase in fibrinogen, hyperglobulinemia, and increased viscosity may contribute to thrombus formation.

DIAGNOSIS OF POST-OPERATIVE THROMBOSIS

The diagnosis of frank thrombophlebitis is usually not at all difficult, and the tender, swollen extremity associated with chills and fever is characteristic. The diagnosis of the early bland thrombosis or phlebothrombosis is much more difficult, and requires careful observation of the patient. An unexplained rise in the pulse and/or the temperature may be the first warning sign and demands careful examination of the legs (Allen et al.¹⁶). Bauer⁶ has called attention to the symptom of restlessness and we have been impressed by this as an early symptom. The patients have a sense of "something being wrong," they are restless and worried. Aching or cramp-like pain in the calf may be the first warning. Examination may reveal tenderness in the calf and pain with dorsiflexion of the foot (Homans), the muscles may be tense or spastic and there may be cyanosis of the foot which is evident in dependency and in some early cases, evidence of vasospasm, i.e., coolness and hydrosis. In the early stage, venography has been of assistance in the diagnosis but venograms are difficult to interpret and the diodrast may be irritating

to the veins. There is a tendency at present to rely more on clinical signs and less on venography in the diagnosis of quiet thrombosis. In spite of the most careful observation, there still remains the patient who has a sudden pulmonary embolus without previous warning of thrombosis. There is urgent need for a clinical or laboratory test to detect incipient thrombosis and it is for this purpose that we wish to present our preliminary studies of prothrombin activity in the post-operative patient.

Our first efforts to find a laboratory test which might be of value in detecting early thrombosis was stimulated by the work of Waugh and Ruddick.¹¹ They used a heparin dilution method of determining blood coagulation time and found the time was decreased during bed rest, in acute inflammatory conditions, in the presence of hemorrhage, and during the post-operative period. Using this method we have found marked reduction in coagulation time in several post-operative patients who developed thrombosis. The test was unsatisfactory for extensive clinical use as it required 12 cc. of blood for each determination and the end point of coagulation was so difficult to read that interpretation of the results was difficult. A decreased prothrombin time was also noted in those patients who developed thrombosis. The determination of prothrombin activity of the plasma is a much simpler laboratory procedure and it seemed worthwhile to study its alterations in the post-operative patient.

There are conflicting reports in the literature concerning the relation of prothrombin activity to thrombosis. Tuft and Rosenfield¹⁷ concluded from their studies using dilute plasma, that an acceleration of prothrombin time is not suggestive evidence of a tendency to thromboembolism. Hurn, Barker and Mann¹⁸ found that the levels of antithrombin and prothrombin are often outside observed normals in patients having a tendency to thrombosis, but that high and low values are present in about equal numbers. Levy and Conroy¹⁹ found decreased prothrombin times during ether anesthesia with a return to normal within 24 hours after the operation. They used the bedside method of determining prothrombin time. The work of Bancroft and Stanley-Brown²⁰ gives support to the thought that prothrombin activity may give a clue to thrombosis. They determined the "clotting index" according to the formula—C.I. equals Prothrombin + Fibrinogen.

Antithrombin

index of 1.0 or over indicated a tendency to thrombosis and one of 0.3 or less, a tendency to bleed. In a series of post-operative patients, 65 per cent had a normal clotting index and an uneventful convalescence. Thirty-five per cent had a high index and although no frank signs of phlebitis developed, this group all had fever and a prolonged convalescence without any demonstrable cause. Patients with phlebitis all had high indices as did seven patients with pulmonary emboli. They studied patients pre-operatively and on the seventh and ninth post-operative days, and believed that a high index indicated a tendency to thrombosis. Shapiro²¹ found a hyperprothrombinemia in patients who had venous thrombosis or a pulmonary embolus. He determined prothrombin time on diluted (12.5 per cent) plasma as well as on whole plasma and found the most consistent decrease in the dilute plasma determination. His results using whole plasma were variable and at times he found a decreased prothrombin activity when thrombosis was actually present. He concluded that a decreased prothrombin time found with dilute plasma was an aid in the differential diagnosis of thrombosis.

METHOD

Our method of study has been as follows:—Prothrombin activity is determined pre-operatively (the morning of operation) and in the evening after operation. Daily determinations are made each day through the sixth post-operative day. This procedure was followed in a series of 68 surgical patients and 122 obstetrical patients. The initial results indicated that values on the third post-operative day were most significant, and a large series is now being studied doing determinations on the first and third post-operative days. The method used for determining prothrombin activity is as follows and is essentially that described by Quick.²²

1. *Preparation of thromboplastin:* A fresh human brain is stripped of vessels, gross blood washed off with normal saline, and the tissue macerated by beating at medium speed in an electric mixer. Water and lipids are extracted with large volumes of acetone at low temperature; usually four changes of acetone are required. The granular mass is then placed in a vacuum desiccator and the acetone removed by oil suction pump. The dry powder is kept in a desiccator under refrigeration. For use, 0.3 gm. of the dried powder is suspended in 10 cc. normal saline and the mixture digested at 50-55° C. for 20 minutes with frequent

shaking. It is then centrifuged at 1500 RPM for 5 minutes and the turbid supernatant fluid pipetted off. This is mixed with equal parts of .024 M calcium chloride solution and the mixture placed in a water bath at 37° C. just prior to use.

2. *Standardization of thromboplastin:* Determinations are run in quadruplicate on two fresh plasma samples from each of five normal individuals. Dilutions of 5, 10, 15, 20, 25, 40, 60 per cent, and whole plasma are used and a curve constructed from the average values. Prothrombin activity of an unknown is calculated from this curve.

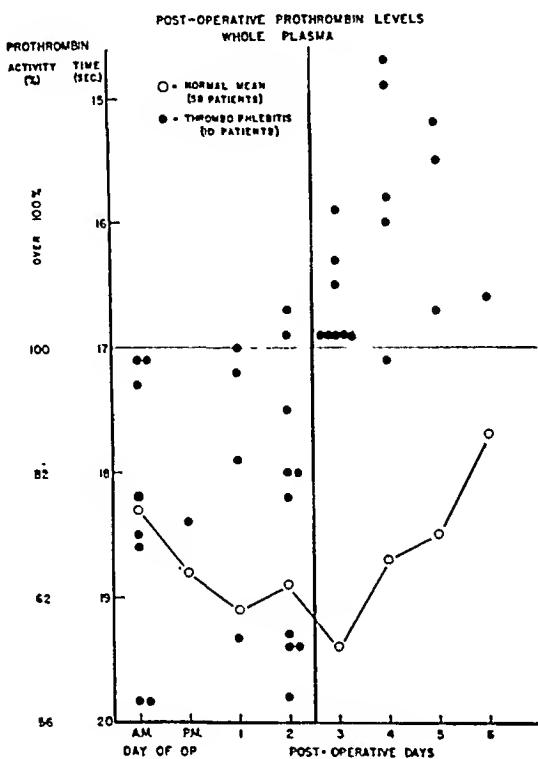
Different individuals may obtain dissimilar results because of differences in reaction time, so they must run checks against each other or carry out separate thromboplastin standardizations. All determinations in this series were done by one individual (R. S.).

3. *Sampling:* Blood is drawn in a dry syringe, avoiding hemostasis as much as possible, and transferred to bottles containing dry oxalate mixture (.006 gm. ammonium oxalate and .004 gm. potassium oxalate in 5 cc. blood). All blood samples in this series were taken by one individual (R. S.) to avoid possibility of error. Hemolyzed or partially clotted blood is not used:

4. *Determination of prothrombin activity:* Blood is centrifuged at 2000 RPM for 10 minutes and the plasma pipetted off. Determinations are run on whole plasma and on plasma diluted to 25 per cent (1:3) with normal saline; 0.1 cc. plasma is pipetted onto a clean watch glass which is placed in the water bath at 37° C. To this is added 0.2 cc. of the thromboplastin-calcium chloride mixture; at this moment the stop watch is started. The mixture is stirred constantly with a glass stirring rod; the end point is reached when clot formation is first observed. A black background facilitates observation of the end point. Determinations are run in triplicate.

OBSERVATIONS

The prothrombin activity of the plasma has been determined in 68 post-operative patients. In 10 of these patients thrombosis developed, and the remaining 58 had no complications. Most of the patients selected were over 50 years of age undergoing major abdominal or chest surgery, or having a history of previous thrombophlebitis. Graph I shows the mean of prothrombin activity in the 58 post-operative patients who did not develop thrombosis. Following operation the pro-



GRAPH I

Hyperprothrombinemia in 10 patients who subsequently developed venous thrombosis. Black dots represent single prothrombin determinations.

thrombin activity decreases (prothrombin time increases) during the first three days and the lowest level usually occurs on the third day. After the third day the level increases and returns to normal about the sixth day. Young individuals have a more rapid return to the pre-operative level—usually by the third or fourth day—and the curves are more variable. Only the average levels of prothrombin activity of whole plasma are plotted on the graph but Table I records the average prothrombin times of both whole and dilute plasma and their statistical variations. There is less variation in the results obtained with whole plasma than with dilute plasma.

The prothrombin activity of whole plasma in patients who developed thrombosis is also shown in Graph I. The ten patients did not

TABLE I

 POST-OPERATIVE PROTHROMBIN LEVELS
 58 NORMAL PATIENTS

Dilution	No. of Patients		Mean		Standard Deviation		Coeff. of Variation	
	100%	25%	100%	25%	100%	25%	100%	25%
Pre-op (A.M.) ..	56	50	18.3	33.2	1.25	2.82	.07	.08
Post-op (P.M.) ..	20	13	19.0	36.7	1.78	2.31	.09	.06
Post-op I	27	21	19.1	35.4	1.27	3.94	.07	.11
Post-op II	32	26	18.9	33.7	1.31	2.58	.07	.08
Post-op III	17	12	19.4	33.3	1.31	2.20	.07	.07
Post-op IV	24	19	18.7	32.0	1.27	2.43	.07	.08
Post-op V	15	12	18.5	33.9	1.79	3.46	0.10	0.10
Post-op VI	8	7	17.7	31.5	1.71	2.27	0.10	.08

Whole Plasma 17.0 sec. equals 100% activity
 Dilute Plasma 29.2 sec. equals 100% activity

all have determinations every day but it is evident that their prothrombin activity varied much more than the normal values on the first and second days and were in general above normal. All of the patients who developed thrombosis were above 100 per cent on the second and third days—two patients on the second and eight on the third day. The increase in prothrombin activity was usually abrupt and was significantly higher in every instance than the values obtained in normal patients. In this group of ten patients, five were treated with anticoagulants and five were not. In some untreated patients, the prothrombin values remained high after the third day but in many the values return to a normal level even though thrombosis is present. A larger series of patients is being gradually accumulated and the results are similar to this group. It appears that a sudden rise of prothrombin activity on the second or more often, the third day is a significant warning of thrombosis. This increased activity has been helpful in non-surgical patients in whom the diagnosis of early thrombosis has been questionable, but once thrombosis is established, the activity has usually returned to normal levels.

DISCUSSION

It is too early to draw far-reaching conclusions from the data which have been presented but the consistent results obtained permit tentative impressions. The hyper-prothrombinemia which has appeared rather uniformly on the third post-operative day in patients who subsequently developed clinical evidence of thrombosis suggests that at this time the thrombotic process is just beginning in small veins. The increased prothrombin activity appears to be a transitory phenomenon as the prothrombin time in untreated patients is often normal during the clinically recognizable phase of the disease. It is possible that the increased prothrombin activity occurs just before actual clotting begins and is a warning that the stage is being set and changes are occurring in the blood which result in thrombosis. Whether or not thrombosis has actually begun when the change in prothrombin activity occurs, this seems the ideal time for the use of anticoagulant drugs.

This warning of impending thrombosis is non-specific in that it seems to be present whenever a thrombus is forming any place in the vascular system. In several patients, the activity has been over 100 per cent and on the following day, a small thrombus has been palpable in an ankle vein which had been used for intravenous infusion during the operation. A positive test appears to be a warning that the patient should be observed carefully and perhaps that prophylactic anticoagulants should be given. It is impossible as yet to judge the diagnostic importance of the test. In the series of patients studied, no one has developed clinical evidence of thrombosis who did not have a positive test. Two patients have had a sudden rise of prothrombin activity on their third post-operative day without developing clinical evidence of thrombosis. Both patients were under 30 years, one had an appendectomy, the other a herniorrhaphy, and both were out of bed and walking on their first post-operative day. It is possible that the test is less significant in young people as the greatest variations in prothrombin activity occur in this age group. Older individuals have more uniform prothrombin activity curves following operation and the change suggesting thrombosis is more pronounced.

It is of interest that the increased prothrombin activity is more uniformly evident in the whole plasma determination than in the dilute plasma which is a more accurate test. If the condition is only hyper-

prothrombinemia, it should be equally evident in both methods. It is possible that some factor other than prothrombin is involved. This is only conjecture and the exact situation has not been investigated.

PREVENTION OF THROMBO-EMBOLIC COMPLICATIONS

The greatest efforts to prevent thrombosis should be directed toward patients in the older age groups as 80 per cent of the complications occur in patients past forty years of age and 50 per cent occur between fifty and seventy-five years (Ochsner,²³ Stich,²⁴ Allen²⁵). Every effort should be made to prevent venous stasis by encouraging active exercise of the patient while in bed and by early ambulation. Fowler's position on the Gatch frame should not be used as it causes constriction and angulation of the great veins. Abdominal distension should be prevented, and deep breathing should be encouraged. The cardiac status of older patients should be improved as much as possible. The operation should be done with minimal trauma, and anoxemia should be avoided. Of greatest importance is the prevention of shock and dehydration which result in sludge formation and increased viscosity of the blood. The prevention of infection is very important. Peripheral vasospasm is a cause of peripheral venous stasis and cold extremities should be treated with heat or other measures to overcome the spasm.

A great amount of discussion now centers about the use of prophylactic vein interruption or anticoagulants to prevent thrombo-embolism. Advocates of either method have published convincing statistics supporting their particular method and at the present time, it is impossible to form an unbiased opinion as to their relative merits. Allen and his co-workers^{16, 25} are the foremost advocates of vein ligation, the Swedish workers (Crafoord, Jorpes and Bauer) have had the most experience with heparin, and Barker^{26, 27} exemplifies the advocates of dicumarol. A comparison of published statistics is given in Table II. These results are all from a series of older patients in whom thrombo-embolism is most common and in operations in which the danger is greatest. Whichever method one prefers, no one can deny that great progress is being made.

In spite of these advances in prophylactic treatment, there still remain many problems. Crafoord and Jorpes' experience with prophylactic heparin seems ideal, but heparin is expensive, it must be given parenterally, and the control of dosage is a major problem if all operated

TABLE II

PROPHYLACTIC TREATMENT OF THROMBO-EMBOLISM
Comparison of Vein Ligation and Anticoagulants

Treatment	Number Patients	Thrombosis and Embolism	Fatal Embolism	Authors
None	302	11%	2.9%	Craaford &
Heparin	325	0	0	Jorpes
None	832†	3.9%	.07% (6 cases)	Edgar Allen
Dicumarol	832	0.4% (3 cases)	0	et. al.
None	458*	12%	5.7%	Arthur Allen
Vein Ligation	458	1.1% (5 cases)	1 case	

† Estimated Complications—Abdominal Hysterectomy.

* Selected cases—Older Age Group.

patients over forty are to receive it. Dicumarol is not expensive, but its dosage is more difficult to control than heparin and requires a trained technical staff. Vein ligation involves a bilateral surgical procedure and we do not know as yet, the late complications of interruption of the superficial femoral vein. We are very hopeful that continued experience will substantiate our present feeling that a sudden increase in prothrombin activity to above normal on the second or third post-operative day indicates incipient thrombosis. At present, the patients having a positive test are given dicumarol in adequate doses. It would probably be more logical to give heparin until the dicumarol effect is evident. For the advocates of vein ligation, this test should help in selecting the cases for treatment.

There has been considerable interest in the prevention of post-operative thrombosis and many reports have shown an impressive decrease in thrombosis and pulmonary embolism. The success of prophylactic endeavors has been properly attributed to the use of vein ligation or anticoagulants but the importance of careful post-operative care must not be neglected. Whenever a clinician becomes interested in this problem the patients are followed more carefully and more attention is paid to general preventive measures such as hydration, leg exercises, etc., which are important factors in minimizing this complication. Also

the difference between control and treated series will be more striking because of alertness in diagnosing thrombosis. There can be no doubt but that many patients have minor thromboses which are completely missed unless attention is being focused on the problem.

At present no final decision can be made as to the relative merits of vein ligation and anticoagulants in the prophylactic treatment. Results in one series of patients treated by both methods are very similar (Table II). The results obtained with heparin and dicumarol are a little better than with vein interruption and the low incidence of thrombosis and embolism in each group is very impressive. There are certain contraindications to anticoagulant therapy which should be carefully observed. It is contraindicated in hemorrhagic diseases and probably should not be used after operations which have a tendency to post-operative bleeding from a large denuded area such as after prostatectomy, Miles operation, and in some chest cases. Dicumarol should not be used in patients with liver disease. Most important of all, neither heparin nor dicumarol should be used unless laboratory facilities are available to carefully follow the course of therapy. Both of these drugs are satisfactory anticoagulants and are usually started simultaneously—the heparin for its immediate effect until the dicumarol effect is evident.

A great advantage of anticoagulants is their general effect on coagulation and they should be effectual wherever thrombosis exists, whereas vein ligation prevents embolism only from the tributaries of the vein distal to the ligature. Also they prevent propagation of a thrombus into tributary and collateral veins. Prophylactic vein ligation is usually performed bilaterally just distal to the profunda femoris vein and is effectual in preventing embolism because of the high percentage of emboli which have their origin from the veins of the leg. It is a relatively simple procedure which can be performed under local anesthesia with little risk. It does not require laboratory control and most patients can be immediately mobilized. The danger of hemorrhage is not a factor. Against vein ligation are possible late effects of ligating the superficial vein such as edema, development of varices, and ulceration. Only by prolonged observation can this feature be evaluated. Also it is difficult for most surgeons to sacrifice a major vein if definite disease does not exist.

It should be emphasized that our experience with the prothrombin activity as a test of incipient thrombosis is limited and no far-reaching

conclusions are being drawn at present. It is difficult to obtain a large series of test cases and this preliminary report is being made so that others may test its efficacy. The abrupt increase in prothrombin activity has occurred on the third post-operative day and seems to be a warning of thrombosis. It is a transitory situation as prothrombin activity is often normal when thrombosis is clinically present. The change is more consistent when whole plasma rather than dilute plasma is used in the determination of prothrombin time. The dilute plasma determination is a more accurate index of liver function and is used to follow patients being treated with dicumarol. Prothrombin activity is not an index of the extent of thrombosis. The test has not been evaluated in patients confined to bed for long periods because of medical conditions or fractures.

CONCLUSION

1. Using Quick's one stage method of determining prothrombin activity, we have been able to detect a significant change in the whole plasma of patients who subsequently showed signs of venous thrombosis.
2. This is suggested as a test for the early diagnosis of post-operative thrombosis and as a basis for selecting patients who should receive prophylactic anticoagulant therapy.

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THE EARLY DIAGNOSIS OF CANCER*

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MOST forms of cancer begin in a single cell or in a small group of cells localized in a single organ or tissue. At this early stage the disease is, of course, perfectly curable surgically if we could but detect its presence. Sooner or later, however, a stage is reached when the disease is so far advanced locally that it cannot be excised, or it escapes as a metastasis through the blood or lymph stream to distant points and the chance of cure is gone. Early diagnosis is in this sense more important in cancer than in most diseases, for it often means the difference between success or failure, life or death.

We may think of the diagnosis of a carcinoma as a drama in three acts. In the first act the patient perceives the signs or symptoms of her disease, and after a varying period of delay, goes to consult her physician. Her perception of her signs or symptoms depends first of all upon her keenness of observation and her sensitivity. An alert, intelligent woman is apt to detect a tumor of her breast long before a dull, stolid individual. Education, too, plays a part. A woman who has learned the significance of a breast tumor and who has been taught to examine her own breasts has a great advantage over one who lacks such education. Here is the greatest opportunity for useful propaganda that the cancer societies have. At some time in the early adult life of every individual she should be taught the chief signs and symptoms of the most common forms of cancer, and the importance of going at once to consult a physician when any one of them is discovered. The cancer societies have not as yet worked out any very good way of accomplishing this.

Unfortunately their propaganda has often taken another direction, one which in my opinion, often actually hinders early diagnosis. It is the propaganda of fear. If you read over the leaflets and magazine

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articles sponsored by the cancer societies, you will find that nine out of ten frighten the reader. I have before me as I write a leaflet distributed by the American Cancer Society which illustrates this point very well. In bold red letters we read "No one is safe from cancer. Every three minutes someone in the United States dies of cancer. No one is safe. There is one chance in eight that you yourself will be a victim of this deadly killer. . . . Cancer is the greatest and cruellest killer of American women between the ages of 35 and 55. . . . Guard those you love. Give to conquer cancer."

Now this may be the propaganda line that is most effective in raising money. But it is not the kind of propaganda that is most apt to help the woman who has discovered that she has signs or symptoms suggestive of cancer. She is already frightened enough without being further terrified by what she reads. She may well be too frightened to face the fact that she may have cancer—too frightened to go to her doctor. In my own studies of the manner in which cancer is diagnosed I have come to believe that fear plays a considerable part in the delay that many patients allow before consulting a physician. Certainly it is the next important factor after ignorance in causing delay.

What our patient in the first act of our drama needs is not more *fear* but more *courage*. She needs to be told, and made to believe, that she can be cured. This is the kind of propaganda that will do the most to persuade her to go at once to her doctor. Let us not lose sight of this fundamental fact. What we are trying to do is to get the patient to go to her doctor at the earliest possible moment.

I should like to see the propaganda of the cancer societies written not by publicity agents, familiar with the technique of raising large sums of money, but by wise physicians, aware of the forces that move sick human beings.

The second act of our drama takes place in the physician's office. The patient has done her part—she has conquered her fear and gone to her doctor. It is now his turn to do his part. He takes his history and examines the patient. If he is to detect cancer, he must *suspect* its presence, for unless he suspects that he is dealing with malignant disease, he will not carry out the diagnostic tests necessary to prove the nature of the lesion. The development of this suspicious state of mind depends upon his alertness and his clinical knowledge of cancer. There is clear evidence to indicate that medical education, as it exists

at present, fails to provide physicians with sufficient clinical training in cancer diagnosis. In a recent study of the manner of diagnosis of breast cancer in patients coming to our clinic, we have shown that about one out of every four patients receives incorrect advice from the first physician she consults regarding her breast cancer. Data from other clinics have yielded similar results. In the face of this factual evidence, medical school authorities have in general continued to deny that there is any need of change in the curriculum. Those who do not realize the need for a thorough revision of the medical school curriculum are living in an ivory tower, unconscious of the realities of the practice of medicine.

While we are trying to change the medical curriculum to improve our training of under-graduates in cancer diagnosis, we feel strongly the necessity of attempting to instruct practicing physicians how better to diagnose cancer, and this afternoon's lecture is a small step in this direction.

The third act of our drama records the steps by which the physician proves the presence of cancer. The action occurs in most instances in a hospital, where the roentgen ray laboratories, operating rooms, and pathology laboratories that are needed for the various diagnostic tests, are available.

It is unfortunately as yet impossible to draw a little blood from a patient in your office and send it off to a laboratory for some sort of analysis that will reveal the presence of cancer. There is no chemical or physical reaction of body fluids or tissues that is diagnostic of cancer. There is a continual succession of such claims, but when tested critically, they have all proved to be false. Some of our newspaper writers add to the confusion by interpreting any statement about cancer as news, and printing it. This is all very well for general topics, but medicine in general and cancer in particular is not a proper subject for hasty publicity. The truth, if it is the truth, can do no harm, but it often takes a long time to establish.

In our own institution we have recently had an example of an entirely unjustified claim of a diagnostic test for cancer. It was claimed that the blood serum in cases of cancer has a fluorescent quality not present in normal serum. Before the claim had been adequately checked, an announcement had been made at a medical meeting which was picked up and given publicity in the newspapers. Careful revalua-

tion of the test in our own clinic has proved that it is of no diagnostic value. Because of the publicity given the test, a good deal of time and money have been wasted on it.

In proving the presence of cancer the physician has only roentgen ray studies and the microscopical interpretation of cells and tissues to rely upon. These are highly technical disciplines requiring skilled specialists. Many smaller hospitals can not provide adequately trained roentgenologists and pathologists, and their lack is one of the greatest handicaps that physicians face today in dealing with cancer. The lack of pathologists skilled in interpreting Papanicolaou smears has but recently been felt in many clinics, even some of the largest. The general lack of pathologists properly trained in the interpretation of frozen sections is less well known but certainly more important. There are methods for preparing excellent paraffin sections within twenty-four hours, a service of great help in expediting the diagnosis and treatment of cancer. Ideally all of these services should be available in every hospital. There is today not only a lack of money to pay pathologists, but a great shortage of adequately trained men. In our laboratory of Surgical Pathology at the College of Physicians and Surgeons, Dr. Stout is doing his part to remedy the situation by conducting a course for graduate training in surgical pathology. An average of twenty-five men are enrolled in it.

We will review the diagnostic problem for each of the most common types of cancer. These are, in increasing order of frequency: Cancer of the lip, the oral cavity and pharynx, the urinary bladder, the ovary, the lung, the rectum and recto-sigmoid, the colon, prostate, stomach, skin, uterus, and breast. The data which I will use as to the incidence of the different forms of cancer are based upon the recent New York State morbidity data.

Epithelioma of the lip: Epithelioma of the lip is about fourteen times as common in men as it is in women. It is, of course, overwhelmingly a disease of the lower lip, the upper surface of which is exposed to the sun. Women today are almost as heavy smokers as men, yet they have far less lip cancer. This fact, I believe, is a strong suggestion that the chief cause of epithelioma of the lip is sunlight. We should therefore look particularly for the disease in out-of-door men, such as policemen, sailors, and farmers. Any change in the epithelium should raise a suspicion of beginning epithelioma. In the

earliest stage of the process the keratin layer piles up to form a scale, or crust, which repeatedly falls and reforms. Eventually, when epithelioma develops from the basal layers of the epidermis and begins to grow down into the corium and finally into the musculature of the lip, induration and ulceration occur. A small wedge biopsy should always be done when any induration or ulceration is discovered in the lip. This is a simple office procedure, best done with a sharp knife after a small amount of novocaine has been injected into the lip.

At an earlier stage, when the lesion consists only of piling up of keratin to form a scale, the best procedure is the excision of the involved segment of the lip surface. At this early stage, biopsy will not show fully developed epithelioma, yet the area of diseased epithelium is a constant threat and had best be removed.

Epithelioma of the oral cavity and pharynx: Epithelioma of the oral cavity and pharynx is three or four times as common in men as in women. It is our clinical impression that it usually develops in patients whose oral hygiene is bad. Decayed teeth and the excessive use of tobacco both contribute to the abuse of the oral mucosa. Such patients usually ignore slight abnormalities in the mouth and only come for diagnosis when the lesion is well advanced and becomes painful. This, then, is a type of cancer in which early diagnosis is theoretically easy but is rarely achieved in practice. Our propaganda for the public should aim at educating the individual as to the importance of good oral hygiene and of consulting a physician at once when any abnormality in the oral mucosa is discovered.

The physician on his part should be suspicious of every erosion, induration, or tumor in the mouth, and should biopsy it forthwith. This is a simple procedure, easily done in the office, with anesthesia obtained by the surface application of 2 per cent cocaine. A wedge of tissue three or four millimeters in diameter, excised with a scalpel, is sufficient.

Dentists often see these mouth lesions first, particularly when they develop around teeth. They are accustomed to see granulomas developing around teeth and in the gums following tooth extraction, and they tend to regard all such lesions as benign. This is not a safe practice, for epithelioma sometimes develops in this guise. All such lesions should be biopsied before they can safely be regarded as granulomas.

Leukoplakia developing in the mouth requires special mention. It is, of course, merely a thickening of the keratin layer of the epithelium, but it often precedes epithelioma. The thin, pale, filmy type of leukoplakia need not cause alarm, but the thicker patches of leukoplakia, which are often seen accompanying the thinner variety, must be regarded as precancerous. They should be excised or destroyed by cauterization. New areas of this dangerous type of leukoplakia will usually continue to develop, and the surveillance of these patients becomes a life time task. In searching for leukoplakia the mouth should be inspected by daylight, not by artificial light.

Epithelioma of the urinary bladder: Epithelioma of the urinary bladder is the next most frequent type of cancer. It is twice as common in men as it is in women. Unless the lesion happens to develop in the trigone area of the bladder, it may be silent until well advanced. Any hematuria, or unexplained pyuria, is an indication for thorough urological study, including cystoscopy. Lesions developing in the trigone may produce disturbances of micturition, and when these occur in the absence of infection, cystoscopy should always be done. Papanicolaou smears made from urinary sediment have given presumptive diagnosis in some instances but the method is not yet thoroughly tested. It cannot replace cystoscopic study of the bladder.

Carcinoma of the ovary: Carcinoma of the ovary is the most frequent type of malignant disease of the female genital organs, excepting, of course, cancer of the cervix. It is a silent disease in its early stages, and is usually not diagnosed until it has produced peritoneal implants or distant metastases. The finding on pelvic examination of an adnexal tumor when there is no history of pelvic inflammatory disease, is an indication for exploratory laparotomy. In this way ovarian tumors may sometimes be diagnosed at an earlier and more hopeful stage. We must admit, however, that the outlook today for early diagnosis of ovarian tumors is very poor.

Carcinoma of the lung: Carcinoma of the lung during the past generation has shown a more marked increase than any other type of cancer. The disease is about four and one-half times as frequent in males as it is in females. In most instances it develops in the bronchi, and depending upon its situation in the bronchial tree, it produces a varying degree of narrowing and obstruction which causes obstructive emphysema, atelectasis, or various types of infection of the portion of

the lung peripheral to the site of the tumor. Cough, chest pain, dyspnea, and expectoration of sputum, which is sometimes blood-streaked, are the most frequent symptoms. Loss of weight and strength and pleural effusion are late symptoms, which do not interest us here. In many of the cases of lung carcinoma, the secondary inflammatory phenomena mask the clinical picture and lead to the mistaken diagnosis of bronchitis, tuberculosis, abscess, or empyema. Graham has emphasized the importance of atelectasis of a lobe of the lung. If it occurs in a man at or beyond middle age who complains of a cough or pain in the chest, the probability of carcinoma is great.

When carcinoma develops in the small bronchi near the periphery of the lung, most of the symptoms that we have mentioned may be absent. The disease is then silent until symptoms develop due to actual invasion of chest wall or to distant metastases.

Any patient who develops cough, expectoration, or pain in the chest which do not subside within a relatively short time should be studied with the possibility of carcinoma in mind. Our first and most important diagnostic aid is, of course, a roentgen-ray examination. If chest films were made routinely of every patient admitted to the outpatient department or wards of a hospital, a number of relatively early cases of lung carcinoma would certainly be picked up. When the lesion is in a bronchus near the root of the lung and has not yet caused atelectasis, it may be entirely hidden by mediastinal structures, but it soon infiltrates radially from the lung root and produces streaks or nodular shadows, extending in a fan-like manner out from the lung root.

In most cases where a suspicion of carcinoma arises, it is desirable to study the bronchial tree after the injection of iodized oil. This is a harmless procedure and often reveals important additional information. The oil should be injected through a transglottic canula or catheter, with the position of the patient so controlled that the oil enters the lobes that are to be visualized.

Bronchoscopy is, of course, the next step. In perhaps 75 per cent of the cases of lung carcinoma, the bronchoscopist is able to see the carcinoma and prove its nature by biopsy.

Recently the Papanicolaou smear method has been used successfully to diagnose lung cancer in a number of clinics. Its success in diagnosis is said to approach, or even exceed, that of bronchoscopy. The method promises to be a very useful adjunct in the diagnosis of

cancer of the lung.

But even with all these diagnostic aids, the number of patients in whom lung cancer is detected at an early stage is exceedingly small. The rich vascular and lymphatic supply of the lung results in early involvement of the lymph nodes of the lung root. When this occurs, it is already, of course, too late. The surgical results are very depressing, except in the small group of lesions which happen to arise in the periphery of the lung and by good fortune are detected early, before the adjacent chest wall is involved.

Carcinoma of the rectum and recto-sigmoid: The late Daniel F. Jones, a great authority on cancer of the rectum, once said that "there is no disease which can be diagnosed more accurately than cancer of the rectum after the patient once presents himself, and yet there are few diseases which are diagnosed so late in their course." The average duration of the symptoms in Dr. Jones' series was eight months. The early symptoms are any change in the bowel habit or sensation, and bleeding. There may be a slight irritation in the rectum, caused by the presence of the growth, which may give the sensation of not thoroughly emptying the bowel, or enough irritation to increase the number of movements slightly. A slight increase in constipation may be a moderately early symptom, but it is more often a late symptom. When partial obstruction of the rectum develops, there is a constant desire to empty the bowel, and frequent small movements, sometimes mixed with blood and mucus, occur.

Bleeding from the rectum in an adult should always suggest carcinoma of the rectum or colon, no matter what the age of the patient. Whenever bleeding occurs, cancer must be positively excluded by digital and proctoscopic examination.

Digital examination should be done with the patient in proper position. The knee-chest position is not the correct position because any tumor which may be present is pulled out of the pelvis and away from the examining finger in this position. Either the Simms or the lithotomy position is much to be preferred. At least four out of five rectal carcinomas are within reach of the examining finger and can be detected by careful digital examination.

If nothing is found by digital examination, the next procedure required is examination with a sigmoidoscope. This will reveal a carcinoma anywhere below the middle third of the sigmoid, with the

exception that some carcinomas of the recto-sigmoid junction are impossible to see because of the fixation of the lesion to the sacrum and the constriction of the bowel. The fixation of the bowel and the presence of the solid mass can, however, be detected with the sigmoidoscope, and are sufficient evidence for exploratory laparotomy.

Biopsy should always be done when a lesion is discovered.

All patients with symptoms consistent with carcinoma of the rectum or sigmoid should also be studied with a barium enema. By this means a positive diagnosis can often be made, although it must be kept in mind that carcinomas at the recto-sigmoid junction, even when they are well advanced, are sometimes impossible to detect by X-ray study, and a growth in this situation is more likely to be missed than one in any other portion of the large intestine.

Polyps in the rectum and recto-sigmoid provide a special problem. They should always be biopsied if they show suspicious changes, and even if they appear innocuous, they should be excised, for they must be regarded as a precancerous lesion.

The problem of differentiating between carcinoma and diverticulitis of the sigmoid frequently arises. The evidence obtained from barium enema is often the deciding factor. Sometimes carcinoma cannot be ruled out and exploratory laparotomy has to be done. Even then, the surgeon may have great difficulty in deciding what he is dealing with. The inflammatory phenomena secondary to perforation of the bowel are very confusing.

Our hope for earlier diagnosis in carcinoma of the rectum and recto-sigmoid depends primarily upon education of the public to consult physicians when abnormal bowel habits develop, and upon educating physicians so that they will never omit digital, sigmoidoscopic, and roentgen-ray examination in these patients. Unfortunately, it is a fact that we continue to see many patients with cancer of the rectum who have consulted one or more physicians without ever having had a rectal examination. Hemorrhoids are sometimes removed without the true cause of the bleeding being discovered.

Carcinoma of the colon: Carcinoma of the colon is somewhat more common in women than it is in men.

These lesions, from the viewpoint of their symptomatology, fall into two broad groups. Those situated in the cecum and the right half of the colon do not commonly obstruct, for in this part of the

bowel the lumen is large and its contents still liquid. The symptoms which these tumors produce are therefore chiefly due to ulceration, bleeding and infection. Anemia is the commonest symptom and it may be of very marked degree. It is probably caused by the large size of the bleeding surface which these tumors present, for nowhere else in the body are carcinomas with such a large ulcerated surface to be found.

Unexplained anemia, with or without gastrointestinal symptoms, or a right-sided abdominal mass, is an indication for X-ray study of the bowel by barium enema. The so-called double contrast method of examining the colon is an important part of the X-ray study because only in this way can polyps be demonstrated or ruled out with certainty. It is important that a barium enema be given before barium is given by mouth in all cases in which carcinoma of the colon is suspected, because barium given by mouth may plug a stenosing carcinoma and cause complete obstruction.

In carcinomas of the left half of the colon, the obstructive symptoms predominate. Here the lumen of the bowel is smaller and its contents are semi-solid, and the carcinomas which develop in it are often annular and constricting. Our best hope for early diagnosis of these left-sided carcinomas of the colon is barium enema study whenever there is any change in the bowel habit. Even when the symptoms have been present a long time, and obstruction is relatively well developed, the carcinoma may be localized to the bowel and surgical cure easy.

Carcinoma of the prostate: Carcinoma of the prostate is the third most frequent type of cancer in males. From the viewpoint of early diagnosis, however, it presents the greatest problem of all. The earliest symptoms are frequency and difficulty in urination, but these do not usually develop until the disease has infiltrated tissues beyond the prostatic capsule and is well advanced. In the great majority of patients with prostatic carcinoma the disease is so far advanced when the patient is first examined that there is no question about the diagnosis. Cure is rarely, if ever, obtained in these cases by even the most radical surgery. Yet our only hope for earlier diagnosis is the detection by digital examination of small areas of induration in the prostate. We must face the fact that there is at present no practical way of accomplishing this.

Carcinoma of the stomach: Carcinoma of the stomach is the most frequent type of cancer occurring in the male sex, and it is also comparatively frequent in females. The disease is a particularly insidious one, and provides a problem in early diagnosis for which we have found no solution. In the early stages of the disease symptoms are usually ill-defined. Some patients have no symptoms at all; others may have slight epigastric distress or some loss of appetite, or a feeling of loss of strength and inability to get through the day's work.

There is in addition, a group of patients who develop gastric cancer after a long history of attacks of indigestion characteristic of chronic ulcer. In this group, the diagnosis of carcinoma is equally difficult, because it is natural to attribute the new symptoms to the old ulcer. In a patient with an ulcer history, any change in the character of the symptoms should at once raise a suspicion of the onset of carcinoma.

Alvarez analyzed the histories of forty-one physicians with carcinoma of the stomach and showed that even they, who were presumably aware of the possibility of cancer of the stomach, did not obtain a correct diagnosis any sooner than the average layman. If physicians fail to diagnose the disease soon enough in themselves, it is difficult to see how we can hope for improved diagnosis in their patients.

Once a physician suspects that his patient may have carcinoma of the stomach, it becomes his duty to exclude the presence of the disease. Analysis of the gastric contents is probably the least important of the several diagnostic procedures which should be carried through. It has been shown that in many cases of carcinoma, acid is still present, although the majority of patients with the disease have achlorhydria.

Roentgen-ray examination is by far the most important method of diagnosis, but even with this method, the diagnosis of a small carcinoma, particularly of the spreading and infiltrating type, may be extremely difficult for the roentgenologist, particularly when the growth is located in the fundus. He has to rely in his differential diagnosis to a considerable extent upon changes in the mucosal folds of the stomach. Carcinoma infiltrates and obliterates these folds. Unfortunately, the inflammatory process associated with peptic ulcers of the stomach sometimes also obliterates the mucosal folds. In lesions of the antral region, the roentgenologist's greatest difficulty is in differentiating carcinoma from antral gastritis. It is particularly in this group

of cases that gastroscopy is likely to give valuable information which assists in the differential diagnosis.

It is also difficult to distinguish ulcerating carcinoma from peptic ulcer in certain cases. Carcinomas sometimes develop in the margins of peptic ulcers and confuse the roentgenologist.

The flexible gastroscope, although it has been in use only a few years, has proved to be of considerable value in differential diagnosis of lesions of the stomach. The great handicap of the method is the discomfort of gastroscopy which, even when skillfully done, is a relatively trying procedure.

With all these diagnostic aids at his command, the clinician is still unable to diagnose carcinoma of the stomach correctly in a considerable percentage of the earlier cases. Diagnostic difficulties are greatest in the group of patients who have had gastric symptoms for a long time. This fact is illustrated by the frequency with which the resected stomach shows carcinoma, even though the preoperative diagnosis after careful clinical study was benign ulcer. In a number of well studied series of cases of this kind, carcinoma was found in about 20 per cent. Even at the operating table, with the abdomen open and the stomach wall between his fingers, the surgeon is often unable to decide whether or not carcinoma is present.

In years gone by, surgeons hesitated to explore and resect the stomach in these cases because of the high operative mortality, but today the operative mortality for resection in favorable cases is under 5 per cent, and most surgeons are agreed that the wise thing to do if there is any question about the diagnosis is to resect. It is also generally agreed that all supposed ulcers of the greater curvature should be resected, for the great majority of these lesions are carcinoma. Marshall and Welch² have recently suggested that all supposed ulcers of the stomach should be resected.

• The therapeutic test of the effect of medical treatment is of great importance. If the symptoms are not completely relieved, and if blood has not ceased to appear in the gastric contents or feces, and if the crater of the ulcer has not diminished considerably in size and depth during three weeks of adequate medical treatment, operation should be done. If under continued medical treatment the supposed ulcer fails to heal completely, operation is also indicated.

The inadequacy of our methods of detecting cancer of the stomach

in an early and curable stage is shown by the fact that the disease is usually so advanced when exploration is done that resection is possible only in from 15 to 20 per cent of patients. The others are hopelessly incurable when they first consult their physician.

Epithelioma of the skin: Epithelioma of the skin is the second most frequent type of cancer in the male, and the fourth most frequent type in women.

Leaving aside the rare melanomas, which are so uncommon that they do not make much of an impression on data relating to skin cancer as a whole, it is fair to say that this is a kind of cancer that is so easily diagnosed and so easily controllable by good treatment that few deaths from it should occur. Unfortunately, we are far from attaining this ideal.

Patients, of course, often neglect skin cancer until it is well advanced, but we must also admit that physicians not infrequently fail to biopsy every suspicious induration or ulcer of the skin, and thus miss the chance of detecting the disease early. If this simple rule of biopsying every suspicious lesion were only followed, we would at once make a great advance in the control of skin epithelioma. It requires a certain degree of experience to distinguish senile keratoses and other benign lesions from epithelioma, but the physician who lacks this experience can perfectly well overcome his handicap by taking a biopsy. This is a simple office procedure, best done with a small, sharp knife after injection of a little novocaine adjacent to the lesion. Biopsy does no harm, and it has the great advantage of clearly establishing the nature of the disease so that appropriate treatment can be planned.

An exception to this rule is, of course, in lesions which are so small that it is convenient to excise them for biopsy in their entirety, together with an adequate margin of adjacent tissue. This implies an excision extending at least 5 mm. wide of the margin of the lesion on every side.

We feel that it is wrong to treat lesions of the skin of questionable nature by fulguration or by radiation without biopsy. If the lesion is an epithelioma, the treatment may not be radical enough. If it is benign, the treatment is needlessly drastic.

There is a great advantage in lesions of the skin, as elsewhere, in knowing surely and exactly the nature of the neoplasm. The habit of mind that insists on securing this information is more important than anything else in determining early diagnosis as well as good treatment.

Carcinoma of the uterus: Cancer of the uterus is, of course, one of the commonest forms of cancer in women. The cervix is affected about three times as frequently as the corpus.

Carcinoma of the corpus usually occurs after the menopause, when any uterine bleeding is a very suspicious sign and is an absolute indication for dilatation and curettage, to rule out carcinoma. In women who have not reached the menopause, irregular bleeding or spotting between periods, or excessive bleeding should also suggest the possibility of carcinoma of the corpus. A thin malodorous discharge is sometimes present. Dilatation and curettage are indicated if these symptoms persist.

In carcinoma of the cervix, vaginal discharge or abnormal bleeding are the usual symptoms. Inspection will usually reveal a suspicious erosion or fungating tumor of the cervix, and the diagnosis is easily made by taking a small biopsy with a simple biting forceps. When the disease is very early, and occupies only a small superficial area on the surface of the cervix, or when the lesion is hidden within the cervical canal, its detection may be difficult.

It is probably true that the only recent advance in the early diagnosis of cancer that has been made is in relation to epithelioma of the cervix. I do not refer, as you might think, to the Papanicolaou smear method of diagnosis, but rather to the discovery of the significance of the lesion which has come to be known as *carcinoma in situ*. It was about fifteen years ago that alert gynecological pathologists in several different clinics began to make the microscopical diagnosis of carcinoma in situ in the cervix. In this lesion the epithelium is thickened, but there is no downgrowth or invasion of the underlying stroma. The individual proliferating cells however, are hyperchromatic, vary abnormally in size and shape, and have all the characteristics of cancer cells. When these lesions first came to the attention of gynecologists, there was endless discussion as to whether or not they were malignant or benign. Today, because of the careful follow-up of patients with these lesions, and because of exhaustive microscopical studies of the lesions, it seems clear that carcinoma in situ in the cervix may be the initial phase of the development of ordinary cervix cancer. It probably exists as carcinoma in situ for a long time before it evolves to become infiltrating epithelioma. These facts have been established largely by work in the Women's Free Hospital in Boston, by Young, and in the Gynecological Clinic at Johns Hopkins by Te Linde.³ In both Young's and Te Linde's series of

cases of carcinoma in situ, the average age of the patients was about thirty-five years, while the average age of fully developed carcinoma of the cervix was forty-eight. Both Young and Te Linde followed several patients with carcinoma in situ in which no treatment was given, and proved that the lesion eventually evolved into typical infiltrating carcinoma of the cervix. In both Young's and Te Linde's series, many of the patients who had carcinoma in situ were also found to have fully developed infiltrating carcinoma in other portions of the cervix when the uterus was removed and carefully studied.

Young has shown with beautiful kodachrome photographs that carcinoma in situ may be present in an apparently innocuous, simple erosion of the cervix, and that a faint spotty redness of the cervical mucosa is sometimes the only sign of its presence. In the great majority of cervices in which it was detected, the examiner had no suspicion that it was present. It was discovered only because Young and his colleagues biopsied almost every cervix that they examined. They used the Schiller test to indicate areas of abnormal epithelium, noted these with care, and took a biopsy from each with a biting forceps.

With this method of studying the cervix, namely, staining it with Gram's iodine and biopsying the suspicious areas, it would seem that it might be possible, if the examination were repeated at yearly intervals, to detect most carcinomas of the cervix while the disease is in a very early and easily curable stage. If this is true, the method offers a way of controlling cancer in the cervix which would make the disease as easily controllable, as, for instance, cancer of the skin. . .

We must, of course, also speak of the Papanicolaou smear test. The fact has been well established that these smears will often reveal carcinoma in the cervix when it is hidden from sight within the cervical canal, or when it is masked by an apparently innocuous erosion. In a series of 8,636 women in whom Papanicolaou smears were done, Jones and her associates reported finding nineteen carcinomas of the cervix which were not suspected clinically.

In Young's experience, however, the Papanicolaou smear was negative in about 30 per cent of the cases of carcinoma in situ which he discovered by routine biopsy. If the smear method had alone been relied upon, the disease in these women would have been missed. It is also well established that the smear method sometimes gives false positives. It would therefore seem that biopsy is a more reliable method of detecting

carcinoma in situ. At least for the present, it is more important to encourage routine biopsy than routine Papanicolaou smear. Finally, the microscopical interpretation of the Papanicolaou smear is more difficult than the interpretation of biopsy specimens, and few pathologists are at present qualified to interpret them.

Carcinoma of the breast: Cancer of the breast is twice as common as any other form of cancer. One woman out of twenty-five, according to our New York State data, will develop cancer of the breast some time during her life. This startling figure has recently been confirmed by morbidity data from Connecticut.⁴ If he is to detect cancer of the breast successfully, a physician needs time in which to examine his patient and a good light in which to study the contour of the breasts. As carcinoma cells grow in the breast, they stimulate the proliferation of fibroblasts, not only in the tumor, but in the surrounding breast tissue. As the fibroblasts age, they contract, and through their connection with the fibrous septa of the breast which reach the overlying skin, as well as the underlying pectoral fascia, a whole series of retraction signs are produced. If I had time, I should like to illustrate these for you, but lacking that, you may see them illustrated, if you wish, in a forth-coming paper in the *Journal of the American Medical Association*. These retraction signs not only include the simple dimple over the tumor, but changes in the contour of the breast, elevation of the breast as a whole, distortion of the areola, deviation of the axis in which the nipple points, and flattening or retraction of the nipple. Bleeding from the nipple is only very infrequently a sign of carcinoma. It is usually caused by an intraductal papilloma. These papillomas, of course, must be excised and the possibility of carcinoma ruled out.

Any erosion of the nipple, no matter how small, is usually a sign of the Paget's type of breast carcinoma. This is merely a special type of breast cancer in which the carcinoma cells grow along the ducts from the primary tumor in the depths of the breast to reach the surface of the nipple. Every erosion of the nipple should be biopsied to exclude Paget's disease. When the diagnosis is confirmed, radical mastectomy should of course be done, just as for every other type of breast carcinoma.

There are so many benign lesions which closely simulate the clinical picture of breast carcinoma that biopsy often has to be done. Fat necrosis, the so-called sclerosing adenosis, and many other lesions produce

signs which may be indistinguishable from breast carcinoma.

Dr. Stout and I, at the College of Physicians and Surgeons, believe that incision biopsy is the best method. Through a small incision directly over the tumor, with careful hemostasis so that the lesion is well seen, we excise a tiny wedge of tissue from the surface of the tumor. The wedge need not be more than 3-4 mm. in diameter. This is sufficient for the preparation of a frozen section which gives us, almost without fail, a sure and certain diagnosis. In rare instances the frozen section is not decisive and we have to wait twenty-four hours for a paraffin section.

This kind of biopsy, of course, requires hospitalization of the patient and preparation for a radical mastectomy, should it be necessary. All this is desirable because thus both patient and surgeon are fully prepared for whatever may be required.

We disapprove of the aspiration method of biopsy for several reasons: In the first place, it is rough. Plunging a large bore needle several times into a firm carcinoma requires a good deal of force, which, we fear, may favor metastasis. Our first requisite in dealing with carcinoma is gentleness. Some time during the natural history of many breast carcinomas an embolus gets loose into the general blood or lymph circulation and hope of cure is gone. We do our best to avoid being an agent in this process.

Our second objection to aspiration biopsy is that it does not provide satisfactory microscopical evidence. The microscopical differential diagnosis of some of these breast lesions is very difficult, and the pathologist has a much better chance when he has a good sized section which shows the architecture of the lesion, rather than a smear showing only a few cells.

A third objection to aspiration biopsy is that the diagnostician cannot be sure that his needle is in the carcinoma. If he gets only nearby tissue cells in his needle, he may get a negative report and send his patient away with an undiagnosed carcinoma.

There are no new advances in the diagnosis of cancer of the breast, but we have yet a long way to go in utilizing to their fullest extent our present knowledge and proved methods of careful clinical and microscopical study of the breast.

Cancer Detection Clinics: A new development in the diagnosis of cancer is the cancer detection clinic. Since Dr. L'Esperance first organized a clinic of this kind at the New York City Infirmary in 1937, some

500 cancer detection clinics have sprung up in this country. The public interest has been whipped up by the propaganda of the cancer societies for these clinics, and the response from the public has been so marked that some of the cancer detection clinics are booked up with appointments for many months in advance. The aim in the cancer detection clinics is, of course, the diagnosis of unsuspected and symptomless cancer. Many of those who apply for examination, however, have symptoms referable to a specific organ or system. They have had their symptoms for some time, but fear or negligence has prevented them from consulting anyone. The cancer propaganda crystallizes their fear, and they rush off to the cancer detection clinic. We must, of course, recognize that the cancer propaganda is the immediate factor in making them seek medical care.

The point to be argued is not whether we favor propaganda urging people with or without symptoms to have physical examinations aimed at detecting disease, including cancer. We are of course in favor of this kind of preventative medicine. The question is rather, who ought to perform these examinations—local physicians or the staffs of cancer detection clinics. This is a complex question which must be considered from the viewpoint of what is best for the efficient organization of the practice of medicine as a whole, as well as from the viewpoint of which is the most efficient method of diagnosing cancer.

In considering whether local physicians can do as good a job of diagnosing cancer as the cancer detection clinics, it is important to divide cancers into two classes, the *accessible* and the *inaccessible* ones.

The first group includes, for example, cancers of the breast, cervix of the uterus, the skin, the prostate, the rectum, the lip and the buccal cavity. The diagnostic procedures required for the detection of these forms of cancer are relatively simple. They can be carried out in a physician's office and are certainly within the scope of any properly trained physician. The inaccessible forms of cancer include, among others, cancers of the stomach, colon, lung, pancreas, and ovary. The detection of these types of cancer is often exceedingly difficult, and indeed is impossible in many cases. Complex and expensive laboratory and operative procedures are required, such as gastrointestinal roentgen-ray study and bronchoscopy. These are, of course, not ordinarily available in doctors' offices. The local physician has to refer his patient to a hospital or special diagnostic laboratory for help in searching for these inaccessible

forms of cancer.

But what has been the achievement of the cancer detection clinics with these *inaccessible* forms of cancer? I have carefully studied the available reports from cancer detection clinics, and I find no evidence that they have had any significant degree of success in diagnosing the inaccessible forms of cancer. Dr. L'Esperance⁵ reported that forty-eight cancers were found among 4,105 new patients examined during 1944 and 1945 in the Strang Cancer Prevention Clinic. Nineteen of these cancers were in the skin, nine in the breast, and six in the cervix. Fourteen others were listed as miscellaneous.

In five cancer detection clinics sponsored by the International Cancer Research Foundation in Philadelphia,⁶ 5,279 women and 877 men were examined between 1944 and 1946. Cancer was found in five of the men; three having carcinoma of the prostate, one chondrosarcoma of the ilium and one carcinoma of the lung. Nineteen of the women were found to have cancer; five had carcinoma of the breast, four carcinoma of the cervix, three carcinoma of the fundus of the uterus, three epithelioma of the skin, one melanoma of the skin, one carcinoma of the gall bladder, one abdominal carcinomatosis, and one carcinoma of the skin.

It will be noted at once that neither of these reports claims the discovery of a single case of carcinoma of the stomach or colon. The reason, of course, is simply that examination has not included roentgen-ray studies. They would be too expensive for any cancer detection clinic to attempt routinely. Yet these are the most important types of cancer in which the cancer detection clinic might be able to offer the patient something that the general practitioner could not.

In our own hospital, Drs. Swenson, St. John and Harvey⁷ have recently studied the frequency of symptomless gastric cancer in presumably well people. Dr. Swenson examined a total of 2,432 symptomless patients, over the age of fifty, fluoroscopically. His method was to do a rapid fluoroscopic examination without taking any films. In this way, with the help of two assistants and a stenographer to handle the patients, it was possible for him to examine as many as forty patients an hour. Three patients were found to have malignant gastric tumors, two of which were carcinomas and one a lymphosarcoma. The two carcinomas which were found had not metastasized, and resection was done with a good prognosis.

From this evidence it would appear that roentgen-ray studies would reveal at least one unsuspected carcinoma of the stomach in each thousand patients examined. When we face the hard fact of whether or no society is willing to assume the cost of such an undertaking, we must pause and estimate how much a human life is worth in dollars and cents. At our ward rates of \$10.00 for a gastrointestinal series, detecting a single gastric carcinoma would cost \$10,000. At our private patient rates of \$60.00, it would cost \$60,000. Assuming that the actual cost lies somewhere between these two figures and is perhaps \$30,000, it is doubtful that the method is practical. Until some more economical method of detecting gastrointestinal cancer is discovered, the Cancer Detection Clinics are as helpless as the local physician.

While Cancer Detection Clinics have no advantage in the diagnosis of the inaccessible forms of cancer, they present a serious disadvantage from the viewpoint of the efficient organization of medicine as a whole. The propaganda for the Cancer Detection Clinics infers that practicing physicians are not capable of diagnosing cancer, and undermines the confidence of the layman in his local physician. This is unfortunate, for the diagnosis of disease in general is the responsibility of the general practitioner. Cancer is only one of the great diseases. We cannot contemplate taking away from the general practitioner his role in diagnosing it, or at least in putting his patient on the road to diagnosis. To do so would upset the whole balance of medical practice. If we carried out the principle of providing special facilities for the diagnosis of each one of the great diseases, we would entirely disrupt the practice of medicine. We would have clinics for the detection of heart disease, arthritis, cancer, diabetes, and so on, ad infinitum, and patients would rush from one clinic to another without any guidance. The waste of time and energy on the part of both physicians and patients would be beyond calculation. The general problem of the diagnosis of disease must and should remain in the hands of the well-trained general practitioner and internist. He should be the first to be consulted, and it is his duty to guide the patient to specialists if they are needed to carry out special diagnostic procedures or treatment.

To sum up the role of cancer detection clinics, we recognize the fact that the accessible types of cancer will be diagnosed in them if patients are solicited by the propaganda methods now widely used. We believe, however, that this is a task within the capabilities of the general

practitioner and internist and that the cause of good medicine in the broadest sense of the word is better served by urging patients to go to their local doctor than to go to special cancer detection clinics. He should be perfectly capable of doing a careful general physical examination and of detecting the accessible cancers. The inaccessible types of cancer, such as cancer of the stomach and colon, can be diagnosed only by expensive and highly technical methods. The cancer detection clinic can do no better for them than the local doctor. We must face the fact that we lack satisfactory methods for diagnosing inaccessible types of cancer. We should not, moreover, attempt to conceal this fact from laymen. We need the full understanding and sympathy of the public in whatever we attempt to do. These are the reasons why we have not opened a cancer detection clinic at the Presbyterian Hospital.

There is one provision that we must make when we reject the idea of the cancer detection clinic. It is that opportunities for the continued education in cancer diagnosis of the physicians now engaged in the practice of medicine be made available. Free post-graduate courses must be provided by the medical schools and hospitals where the general practitioner can learn the new diagnostic methods, such as those for carcinoma of the cervix. In this way the general practitioner can keep abreast of medical progress and offer his patients the best chance for early diagnosis.

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THE SURGICAL TREATMENT OF CANCER OF THE CERVIX UTERI*

(*A Radical Operation for Cancer of the Cervix*)

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CARCINOMA of the cervix is a relatively superficial lesion and, therefore, should be detectable early in its evolution. Measures for local destruction of these growths should prove highly effective in the early stages. The problem of propaganda among the laity leading to systematic examination of large groups of asymptomatic patients to detect early carcinomas of the cervix is a vital one but is beyond the scope of this discussion.

In the past three decades irradiation therapy has achieved a predominant position in the treatment of cervical cancer in this country, Canada, South America, England and most countries on the continent of Europe. It is generally held that most patients could be cured of carcinoma of the cervix by irradiation therapy properly conducted if these patients could be first seen in the earliest stages of the disease. The fact remains that the majority of patients when first seen, do not present the earliest stages of the disease and this situation is not likely to change very appreciably in the next few decades.

A review of the results achieved at the Memorial Hospital in the treatment of cancer of the cervix by irradiation from 1934 to 1941, reveals a more or less static situation in that about 28 per cent of all patients, year after year, were afforded a five year survival.¹

Therefore, since the majority of patients developing cancer of the cervix continue to die of this disease, it follows that some consideration might be given to other forms of therapy. The only other form of therapy of proven efficacy is surgery. The objection might be raised

* James Ewing Memorial Lecture delivered before The New York Academy of Medicine, May 6, 1948 at its Stated Meeting.

that this has been tried and found wanting. In answer to this objection it may be pointed out that the surgery that has been tried was of a previous era and that the surgery of the present day has not been systematically exploited in the treatment of cervical cancer. It follows, therefore, that the position of modern surgery in relation to the problem of cervical cancer might be redefined at this time and this is discussed under several headings as follows:

1) *The natural course of carcinoma of the cervix.* This neoplasm, in its earlier stages, is strictly a local lesion. It spreads first by lymph channels to the parametrial nodes and nodes of the lateral pelvic wall and by direct extension to the vaginal vault, later producing discrete vaginal metastases. Finally, there is direct spread into bladder and rectal colon, metastases occur beyond the pelvis in periaortic nodes, liver, lungs, and bones. A feature to emphasize is the fact that in general cervical cancer does not rapidly spread to distal areas but apparently remains localized for relatively long periods. This is well illustrated by the sixty-five necropsy protocols from the Department of Pathology of the Memorial Hospital of patients dying with cervical cancer; 50 per cent of these had no gross evidence of the disease beyond the pelvis at death. They had succumbed from uremia, due to compression of the ureters, or from infection. Studies from other institutions have shown similar findings.²

Thus, carcinoma of the cervix is a lesion which remains relatively localized for prolonged periods; is not, as are some forms of lymphoblastoma, a systemic disease from the onset and does not, as does carcinoma of the stomach or pancreas, present distant metastases in the large majority of instances at the time the clinician first encounters the disease. Therefore, it would appear to be a lesion that is favorable for surgical attack.

2) *The operation for wide resection of carcinoma of the cervix.* The so-called Wertheim operation represented what was regarded to be the maximal of radical surgical attack upon cervical cancer in the early decades of this century. In principle, it consists of resection of the uterus, upper vagina and parametria. The operation as can be witnessed to-day in the Viennese gynecological clinics is a radical supravaginal panhysterectomy with limited parametrial excisions and does not include excision of the paravaginal tissues nor the lymph nodes along the external iliac and hypogastric vessels or obturator fossae.

Macroscopically involved nodes along the external iliac or hypogastric vessels are not systematically resected 'en bloc' with the uterus and parametria. A study of the illustrations accompanying the original article published by Wertheim in 1900, shows the variation in extent of the resections.³ In some, just the uteri, adnexae and limited portions of broad ligaments were removed. In others, more of the parametria was resected, with a limited segment of ureter in certain instances.

The illustrations published in several American and foreign texts of the Wertheim operation show more or less the same procedure. In one important point, there is also a general similarity of description and that is that the lymph nodes from about the great pelvic vessels are to be excised *after* the uterus and adnexae are removed in some instances or are to be excised as individual nodes or groups of nodes. In Taussig's inguinal adenectomy, an adjunct to irradiation therapy of the primary growth in the cervix, the nodes are likewise resected individually or in small groups.⁴ While such resections, as have been demonstrated, have been effective in permanent control of the disease in some cases, they do not conform to the basic principle of resection 'en bloc', i.e., excision of primary growth, affected organ, and adjacent lymphatics with surrounding tissues.

The English surgeon, Bonney, who throughout the years persistently advocated surgical treatment for cervical cancer, is often credited with being the most radical operator of his time in this field. In 1935, he described and illustrated his operation for American gynecologists.⁵ The essential features are a radical panhysterectomy with parametrial excision performed after incision and opening of the broad ligaments. Much of the upper portion of the vagina is removed. The ureters are exposed from about the level of the origin of the uterine artery to the bladder. After the uterus and upper vagina are excised the question of pelvic lymph node resection is considered. Those along the external iliac vein are removed together with the hypogastric artery, but in early cases only the lymph nodes themselves are to be removed. As another and completely independent step, the areolar tissues and nodes in the obturator fossae are removed, sparing the obturator nerve. At the close of the operation a large flap of peritoneum has been spared in the anterior half of the pelvis and this approximated to lateral peritoneal flaps and to sigmoid, permits of complete peritonealization of the pelvis as a final step in the procedure.

The operation which has been planned and is being carried out at present at the Memorial Hospital for radical excision of carcinoma of the cervix and adjacent lymph node groups is as follows:

(a) Low mid-line incision extending to about 3 to 4 cm. above umbilicus. Palpation of liver, pancreas and periaortic region to ascertain absence of metastases.

(b) Usual retraction of bowels out of pelvis and patient placed in Trendelenberg position.

(c) The right infundibulo-ovarian ligament with vessels is divided. From this point upward the posterior parietal peritoneum is incised to over the bifurcation of the aorta. Areolar tissue and lymph nodes are dissected from above downward along the right common iliac vessels, including nodes and areolar tissue about the bifurcation of the aorta.

(d) The peritoneum over the external iliac artery is divided down to the round ligament which is transected between ligatures just as it emerges from within the abdominal wall. This exposes the right retroperitoneal pelvic spaces. The nodes and areolar tissues from above the external iliac vessels are dissected and wiped or pushed medially. By progressive dissection the areolar tissues and nodes in the deep right pelvic spaces and in the obturator fossa are mobilized and packed mesially. (The obturator nerve is spared.) The origin of the uterine artery is transected between ligatures as it arises from the hypogastric artery; several vesical and vaginal branches may be similarly divided. The large uterine veins as they reach the hypogastric vein are also doubly ligated and divided.

(e) By means of digital, gauze and instrument dissection, the fascia over the levator ani muscles and the arcus tendineus are exposed and "swept clean" of areolar tissues in the depths of the space created by the dissection. The right paravaginal tissues are likewise swept mesially against the right vaginal wall.

(f) The right ureter is now identified at the level of the brim of the pelvis and is freed progressively in the loosened areolar tissue, downward toward the bladder. Great care is exercised not to "shave" the tissues off the ureter completely but a certain amount of periureteral tissue is preserved in order to insure its blood supply. In freeing the lowest segment of ureter, parametrial tissue above it is divided and brought downward underneath it and mesially to preserve its attachments to the remainder of the broad ligament. Perivesical fat on the

posterior and infero-lateral aspects of the bladder is also stripped in continuity with the adjacent broad ligament.

(g) The peritoneal reflection from bladder onto cervix is divided near the midline and by blunt dissection the bladder is elevated. This separation is carried downward for a considerable distance on the anterior vaginal wall.

(h) The steps outlined above (c to g inclusive) are now carried out on the left side, the operator changing his position from the left side of the patient to her right side. Because of the loop of sigmoid colon and its mesentery, exposure of the upper left common iliac vessels is not always easily performed.

(i) The uterus and appended tissues can now be moved from side to side and this facilitates transection of the utero-sacral ligaments at a point lateral to the lower pelvic colon.

(j) The peritoneal fold between uterus and pelvic colon is now completely divided and the colon separated from the vagina. During this step the plane of dissection tends to be much nearer the colon than the vagina. By continuation of the dissection the pelvic colon is liberated almost to the end of the posterior vaginal wall.

(k) The vagina is then transected, as low as possible, the edges of the remaining cuff being secured with hemostats. The specimen is removed. Because almost all of the vagina is removed, the rim of the remaining cuff is deeply placed in the pelvis and its partial closure with one or two interrupted sutures is effected with some difficulty. A hard rubber tube is pushed downward out of the vagina to serve as a drain. Soft rubber drains may also be placed in each side of the pelvis and the lower ends pushed out of the vagina or brought out through the lower angle of the abdominal wound.

(l) Because of the extent of the dissection which literally includes all of the pelvic peritoneum except that lying over the dome of the urinary bladder, peritonealization is not possible nor is it necessary.

(m) Closure of the abdominal wound in layers with soft rubber drains in the lower angle leading to each side of the pelvis.

The operation accomplishes a complete removal of the uterus and adnexae, the entire broad ligaments and paravaginal tissues, the pelvic lymph nodes, lymph channels and areolar tissues about the common iliac, external iliac and hypogastric vessels, the lymph nodes and areolar tissues in the obturator fossae, the areolar tissues on the posterior and

<i>Stage of Disease</i>	<i>Number of Patients Operated Upon</i>	<i>Surgical Mortality</i>
1. Very advanced; extension beyond pelvis. Exploratory operation with or without bowel resection for intestinal obstruction	6	0
2 League of Nations Stage I. Schauta operation	6	0
3 Radical pan-hysterectomy with pelvic node dissection for cancer of cervix in L. of N Stages I, II, and III	37	0
4 Radical operation with excision of portions or all of bladder or with portion of rectal colon for disease in L. of N Stage III	12	1 (8.3%)
5 Complete excision of all pelvic viscera with ureteral implantations into colon and colostomy. Disease in L. of N. Stage III or IV	12	3 (25%)
Total	73	4 (5.5%)
Exclusive of category 5 (far advanced cervical cancer not controlled by previous irradiation therapy and/or conservative operation)	61 patients	1 death (surg. mort 1.6%)

inferior lateral surfaces of the bladder wall. And, finally, practically the entire visceral and parietal peritoneum with its subjacent areolar tissues. The latter feature is important because of the rich lymphatic channels which are here present and in free anastomosis with the lymph channels and nodes in the parametria and along the great vessels of the lateral pelvic walls.

3) *Lymph Node Metastases:* It has been stated that once epidermoid carcinoma of cervix has metastasized to lymph nodes in the parametria or lateral pelvic walls, the condition is beyond hope of cure by irradiation because metastatic carcinoma in lymph nodes can not be destroyed by irradiation. While the chances for cure in this stage by irradiation are not great, I would not agree with the hopelessness of the situation from the radiotherapeutic standpoint if the statistics reported for radiotherapy are correct. Certainly all of the five year cures in Stages I., II. and III. can not have been patients without lymph node metastases. Therefore, in some instances of lymph node metastases the disease has probably been controlled by irradiation.

If one compares the clinical findings in any series of patients with the pathological study of the specimen, it becomes apparent that frequently a small primary growth has given rise to one or two metastatic nodes which are not clinically appreciable. Thus all cases classified as League of Nations Type I. or II. (without parametrial extension) can not be strictly in this group, etc.

In the surgical operation described above, the systematic excision of practically all parametrial and lateral pelvic wall nodes is carried out. This, it would appear, has a distinct advantage over a radiotherapeutic procedure, for conceivably the group of patients in whom there are one, two or a few node metastases without further extension of disease, might have a greater opportunity for cure following 'en bloc' resection than with only irradiation.

(4) *Operability:* In the previous controversy of irradiation therapy versus surgery in the treatment of cervical carcinomia, it was stated that the surgeons exercised considerable selection of their patients. This was undoubtedly true and any degree of fixation of the uterus or even appreciable parametrial involvement often led to a classification as "inoperable." Wertheim and the earlier operators did not hesitate to operate upon some patients with parametrial involvement. Bonney repeatedly declared that a number of so-called Type III. cases were operable and stated that his operability was 63 per cent. Meigs, on the other hand, was interested in a specific phase of the problem, namely, to demonstrate that in selected patients with small lesions, situations in which surgical therapy should prove highly effective, the argument of surgical risk could not be raised as a deterrent to operation. He has amply proved his point and states that 10 to 15 per cent of all cervical cancers are operable. He is, of course, referring to surgery as the treatment of choice in the selected patients with early lesions (League of Nations Type I. and II.) which he estimates constitutes 10 to 15 per cent of the patients first seen in consultation.⁶

Obviously the next step in the exploitation of a surgical attack upon cervical cancer is to ascertain if selectivity may be reduced to a minimal degree consistent with good surgical judgment. At Memorial Hospital, at present, a minimum of selection is exercised. Since September 1947, every patient with cancer of the cervix is evaluated as a surgical problem. If there is clinical or roentgenologic evidence of spread beyond the pelvis (inguinal node involvement is not considered extrapelvic

spread) the situation is, of course, regarded as inoperable. Between September 15, 1947, and April 24, 1948, there have been 81 patients with carcinoma of the cervix, all evaluated as surgical problems. In 73, operation was performed. Thus the explorability rate was 90 per cent. Operation was not carried out in 8 cases because of clinical evidence of extra-pelvic spread in 3 instances; in 2 instances of irradiation failure poor physical condition precluded operation and irradiation therapy was again instituted in attempt at further palliation; in 1 instance the general condition was too poor for any treatment and the disease was in its terminal stages; in 2 instances the patients preferred radiation therapy to operation. Among the 73 operated cases, exploratory laparotomy only was carried out in 6 instances. In 67 patients a radical procedure was performed. Thus the operability rate was 82.7 per cent. It is not implied that operability is synonymous with curability since many of these radical procedures were undertaken for palliative purposes only, a cure being out of the question.

The series referred to is not a large one but in view of the fact that it represents as far as possible an *unselected* group of patients; it is presented here in answer to the question so often raised that any surgical attack upon cancer of the cervix must of necessity be somewhat restrained because of the rather high degree of selection that it is anticipated that the surgeon will exercise.

It has been my experience that the so-called "frozen pelvis" is not necessarily indicative of carcinoma extending in solid sheets from the region of the cervix to the muscles of the lateral pelvic walls. The view from within the abdomen downward, as it were, is very frequently much more hopeful from the standpoint of circumventing the process surgically, than might be expected from bimanual vagino-rectal examination. A free plane of dissection can usually be found in the lateral spaces of the pelvis. In only one instance in this series have I been forced not to carry out excision because of invasion of the fascia over the levator ani muscles which afforded literally a "frozen pelvis."

5) *The question of surgical mortality:* It is the factor of surgical mortality that exerted a great influence in the general adoption of irradiation therapy for cancer of the cervix some years ago. Text books of gynecological surgery almost unanimously caution concerning the high mortality of the radical surgical attack upon cancer of the cervix. The mortality from all major surgical procedures for visceral cancer

was relatively high a few decades ago but by persistent efforts in many directions this has been very greatly reduced.

Bonney's mortality was approximately 15 per cent in 500 somewhat selected cases. Meigs⁶ has shown that with the benefits of modern supportive therapy, the mortality in a series of 91 cases was nil (report published in 1947). However, Meigs' patients, it must be admitted, represent a rather highly selected group, namely, and to use his own words, "they were good risks, thin, young and with tumor involving not more than the complete cervix and part of the vaginal wall." Meigs' studies were conducted with a special objective, that is to demonstrate that in a group of patients with small lesions and in whom, therefore, surgical attack should prove highly effective, the mortality could be brought to such a low point that the factor of surgical risk could not be raised as a deterrent to operation. This point he has very amply proved for the selected group.

In the series of 73 consecutive and unselected patients with cervical cancer referred to in the previous section, the operative mortality was as follows:

The overall mortality in the series is 5.5 per cent. The mortality is confined to the group presenting the most advanced local stages of the disease. These patients had all had one to several attempts at irradiation therapy with or without some form of local operation. In the group of 49 patients who had the radical operation and in 12 instances of which there were additional resection of viscera, the mortality was 2.0 per cent.

(6) *The problem of recurrent and advanced cancer of the cervix.
Palliation by radical surgery in advanced cancer of the cervix.*

Where repeated irradiation therapy with or without some form of conservative operation has failed to eradicate the disease, continued irradiation will offer little opportunity for palliation beyond perhaps a temporary restraint in the progress of the disease. If certain limits are exceeded, tissue necroses may develop which may prove as distressing to the patient as the advancing neoplasm itself. Since cancer of the cervix may be advanced locally and yet not have metastasized beyond the pelvis, radical excision may be envisaged. These operations have been carried out on a number of occasions and may be divided into four categories as follows:

(a) When the disease is apparently still localized to the cervix and upper vagina, a radical panhysterectomy with pelvic lymph node re-

section can still be performed.

(b) When there is local recurrence and invasion of the rectum, a complete excision of the vagina and uterus and invaded portion of the rectum is feasible with reconstitution of the rectum by end to end anastomosis.

(c) When the lesion has recurred and invaded the bladder, the uterus, vagina and entire bladder may be resected with bilateral ureteral implantations into the colon. When only one ureter and a portion of the bladder are involved, the invaded portions alone may be excised.

(d) When the bladder and rectum are both involved, the uterus, vagina, bladder and rectal colon can all be removed "en masse." Patients with such advanced disease can be rehabilitated to almost normal activities, at least for appreciable periods.

Patients who receive extensive resections for uncontrolled cervical cancer can hardly be expected to survive five years or more. The operations are carried out for palliative purposes only and sufficient time has now elapsed to convince me, at least, of their value in this respect. The only other alternative is increased sedation but this does not relieve the distress associated with fistulae and other discomforts due to the presence of large infected neoplastic masses.

In regard to the possibilities of palliation, therefore, surgery would seem to have something to offer after other and more conservative measures have been exploited to the maximal extent and the disease remains and is still progressing.

The combination of surgical and irradiation therapy. The large majority of cervical carcinomas exhibit immediate and appreciable to complete macroscopic regression following properly conducted irradiation therapy. It would appear for the present, at least, to be contrary to good judgment not to take advantage of this fact even in a program to re-evaluate the possibilities of surgery. *A priori*, it would seem that a radical operation carried out in the presence of a regressing neoplasm has advantages over one performed in the presence of a flowering growth. Furthermore, a number of cervical carcinomas form papillomatous masses that bleed easily and are heavily infected. Irradiation will reduce the size and vascularity of these growths and there is a subsidence of local infection. In all of the patients subjected to radical operation for cervical lesions that appear localized to the cervix and its immediate vicinity, intra-vaginal roentgen-ray therapy by means of special

cones is carried out. Three thousand to 3500 r measured in air are delivered to the cervix and in some instances to each parametrium. Where the lesion is more extensive and has not been previously irradiated, the usual pelvic cycles are administered. Operation is performed four to six weeks after the last treatment.

This combination of irradiation and surgery does not cloud the issue as to an improved method for the management of cervical cancer. An extensive experience in purely irradiation therapy of this lesion has been gleaned in many centers throughout the world in the past three decades. The important objective is not to decide which is the better treatment, irradiation alone or surgery alone. This is an academic question. The principal objective is to increase the incidence of cure among all patients who present themselves with carcinoma of the cervix and to devise ways and means of increasing effective palliation when cure is out of the question.

Discussion. I do not concur with the view that a planned program for the evaluation of a modern surgical approach to the problem of carcinoma of the cervix is an experiment in the usual sense of experimentation. This would imply that irradiation therapy has reached such a stage of proficiency that any other form of management is contrary to good judgment and the best interests of the patient. That irradiation therapy still leaves much to be desired in the face of the varied stages of the disease encountered in patients as they present themselves, is generally conceded. Therefore, a program in which radical surgery is the principal arm of attack might better be referred to as another approach to the problem.

Years of extensive experience are necessary to properly evaluate the benefits of surgical treatment for a relatively slowly progressing neoplasm. On the basis of the brief and limited experience that has been recorded above, no conclusions are now possible, and there can be no presumption to recommend alteration in the methods at present generally carried out for the treatment of cervical cancer. All that may be said is that this presentation has been a report of a type of clinical investigation in progress on the problem of cervical cancer.

SUMMARY

1. For reasons enumerated, a statement of the position of modern radical surgery in relation to the treatment of cancer of the cervix is made.

II. A radical operation is described for excision of carcinomas of the cervix that have not involved bladder or rectum. This procedure would appear to be more extensive than hitherto carried out for this type of neoplasm. The 'en bloc' excision of uterus, most of vagina, parametria, areolar tissues and lymphatics of the lateral pelvic walls, and the removal of practically all the pelvic peritoneum except over the fundus of the bladder and on the pelvic colon and its mesenteries, is emphasized.

III. Procedures are mentioned for excision of involved viscera adjacent to the cervix in instances of advanced carcinomas of the cervix. These procedures are capable of affording a degree of palliation not possible by other known measures in the face of previous failure of irradiation with or without conservative operation in these patients.

IV. Data are presented to show that, thanks to modern supportive measures for the surgical patient, selection of patients for operation can be quite appreciably reduced in comparison to the selection exercised in the past, and, what is more important, surgical mortality can be kept at such a level that this can no longer be held as a major deterrent to the surgical approach to the problem of cancer of the cervix.

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COMMUNICATION TO THE EDITOR

New York, September 14, 1948

Dr. Mahlon Ashford

The New York Academy of Medicine

2 East 103rd Street, New York 29, New York

Dear Doctor Ashford:

It has come to my attention that there is the possibility of misinterpretation of two statements in my article on the "Prophylaxis of Cancer" read before the 19th Graduate Fortnight of The New York Academy of Medicine, October 18, 1946 and as published in the BULLETIN of The New York Academy of Medicine in July, 1947. I wish to modify these statements and hope it will make my meaning crystal clear.

The first statement appearing on page 385 of the BULLETIN reads as follows:

"The removal of all precancerous lesions of the skin will save many a life from cancer, as skin cancer is the easiest of all types to cure."

Please substitute the following as more clearly conveying my meaning:

"The early and proper treatment of malignant or suspicious skin lesions will save many lives, for skin cancer offers the greatest opportunity for cure."

The second statement I would like to modify appeared on page 386 of the BULLETIN and reads as follows:

"Any one who has ever had even a single dose of low voltage x-ray to the skin is a possible candidate for subsequent skin cancer."

For this statement I wish to substitute the following:

"Under certain conditions and dosage, x-ray to the skin can produce skin cancer. Therefore this ray should never be used except by experts in this form of treatment. Well trained dermatologists using x-ray in the treatment of skin diseases are experts in this form of therapy."

In order that there may be no misunderstandings of my meanings, I would appreciate it if this letter be given publication in the BULLETIN of The New York Academy of Medicine.

Very truly yours,

FRANK E. ADAIR

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MALCOLM ASHFORD, *Editor*

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PSYCHOLOGICAL PHENOMENA
IN CARDIAC PATIENTS*

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WHEN my former teacher, the late Dr. Richard Cabot, retired from the faculty of the Harvard Medical School to become Professor of Social Ethics at Harvard College, he told me that he was going to keep his office on Marlboro Street for one purpose only and that was to reassure patients who had been informed by their private physicians that they had heart disease. He felt very strongly about the harm that many doctors unwittingly do by making a diagnosis of heart disease in the absence of sufficient evidence. Since those days, which corresponded to the end of World War I, we have learned a good deal about the coronary arteries and the nutrition of the heart muscle. As you know well enough our knowledge is still insufficient. We often cannot be certain whether or not the heart is structurally damaged. In the absence of such knowledge it is natural for us to be cautious. We need to protect not only our patients but, quite justifiably, our own professional reputations. If we warn a man never to run upstairs, never to walk into

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a strong wind, never to lose his temper, we may, to be sure, be protecting his coronary system from one standpoint, although we may be hurting it from another. I do not in the least mean to imply that we should not warn him so, but if we do, we are also almost certainly arousing anxiety in him and unless we protect him, as well as his heart muscle, against insults we are falling short of our obligations.

All this is an old story to you I am sure. I need hardly tell an audience of this sort that a large number of patients who consult their doctors because of complaints centering in the heart do not have heart disease; nor need I tell you that the mention of heart disease terrifies most laymen. It is part of your daily work to make differential diagnoses between symptoms resulting from structural alteration of the heart and those due to anxiety. You know very well that these two states often coexist—that anxiety and tension may increase breathlessness and lower the threshold of pain and of visceral sensations, just as pain and breathlessness may give rise to anxiety and tension. Those of you who have followed the recent studies of Dr. Harold Wolff and his associates¹ realize what we have all suspected, that even the rather trivial emotional disturbances of daily life alter the heart's function, raise the blood pressure and the cardiac rate, increase the stroke volume and, in general, decrease the circulatory efficiency of the heart.

Perhaps it should be pointed out that the symptoms of structural heart disease are remarkably constant from patient to patient. Once these symptoms have been mastered it is pretty safe to say that the other symptoms present are not due to heart disease, but to other causes. An accurate assessment of symptoms is the best means of differentiating between structural damage and cardiac disorders due to emotional disturbance. Such a differentiation is essential to intelligent handling of the cardiac patient, because the treatment in the two conditions may be quite opposed. But one must bear in mind that the patient with structural damage to his heart is, himself, often anxious, and emotionally disturbed and many of his complaints may be the result of this disturbance rather than of his cardiac lesion.

Pain and breathlessness are cardinal symptoms of heart damage but they are both often present in the so-called "cardiac neuroses." What can one say about the difference in character of these manifestations in the two states? Anginal pain, no matter where radiated, characteristically occurs in the mid-sternal line. Cardiac pain associated with anxiety

or tension is much more likely to occur over the apex. Unless a neurotic patient has been briefed by witnessing a true anginal attack he will very rarely complain of mid-line pain. Anginal pain characteristically lasts from one to two minutes and is very quickly relieved by nitroglycerine. Pain associated with anxiety or tension often lasts much longer and although it may be relieved by nitroglycerine, relief is slower in coming. The patient with true angina usually knows what brought on the attack of pain, whether it be due to exercise or excitement, and he will immediately stop doing the thing that caused his discomfort. The other patient usually does not know how to account for his pain—which may come on at any time, even while resting comfortably and while apparently relaxed. Furthermore, the patient with true angina has great difficulty in describing the quality of his pain while the other patient can cite chapter and verse about it.

There are analogous differences in the dyspnea experienced by the patient with structural heart disease and by the patient without. The first is more likely to have panting respirations, the second more likely to feel as if he couldn't take a deep breath. Again, orthopnea is more common in the first than in the second.

Other differences could be enumerated. But these facts are widely known to more enlightened internists. If that is so, what then has psychiatry to offer further to this subject? I think it has a not inconsiderable contribution to make to the management and therapy of your patients.

I should like to discuss with you, therefore, some of the psychological phenomena seen in cardiac patients. Since this subject is a large one and the time allotted to me is limited we shall make better headway by restricting the discussion to three aspects of the problem. These three aspects will also coincide roughly with three age groups. The first group consists of children and young people who suffer from various forms of rheumatic heart disease. The second group consists of people of early and middle age who suffer from so-called "cardiac neuroses" and the third group, which I shall deal with only briefly, consists of people of middle and late middle life who suffer from coronary insufficiency and coronary occlusion. This division into age groups is, of course, somewhat arbitrary but, even if not wholly accurate, it will serve our purpose best if we permit it to stand.

Concerning the first group, composed of youthful, rheumatic car-

diac invalids, I think it is probably accurate to say that their psychological difficulties are, in general, subject to several important variables (omitting for the moment the personal characteristics of the patient himself): One is the severity of the cardiac disability; another is its duration and still another is the nature of the medical management to which these patients are subjected and, perhaps most important of all, the attitude that their parents take toward them and their illness. Whether these patients are seriously disabled or not, certain psychological difficulties invariably arise, especially so if the illness confines them to inactivity or to close supervision for any protracted period.

Let us now consider the nature of these problems: What psychological phenomena are we likely to find? Are they confined to the patient himself? What implications can be gleaned from them as to therapeutic management?

Here is a case in point:

Johnny is the eldest child of three. He is just 13; a skinny, lanky, active, intelligent, good-humored boy. He is well liked at school, a reasonably good student and is very keen on basketball and wrestling. He plays forward on the Junior High School basketball team. He has been no special trouble to his parents and, except for an extremely disorderly room and a great disinclination to wash and bathe, they seldom have to correct him. But he has not gained weight and often seems listless and tired and has looked pale and has had dark circles under his eyes. In addition, he has complained of vague pains in his legs and recently had one or two nose bleeds. All this has caused his mother some concern.

One evening he complained of headache and felt feverish. He had no appetite. He slept poorly and when his mother went in to see him he complained that his legs ached. The next morning she sent for their pediatrician. There seemed no doubt at all about the diagnosis. Johnny's mother, who was well posted in medical matters, said after they had left the room: "What about his heart, Doctor? I saw you listening to it for a long time." The Doctor said: "He has a slightly suspicious murmur; we'll have to watch it and keep him perfectly still for the present." That was easy because Johnny felt too wretched to do anything but lie quietly in bed and take the medicine given him. In a week's time he was a good deal better. But the doctor continued to come every day and always listened carefully to the boy's heart. Johnny was fas-

cinated with the electrocardiogram and the doctor explained all about it to him. His mother stood at the bed-side with her eyes glued on the doctor's face. She was always cheerful and controlled but naturally she was terribly worried. The doctor explained to her that although the valvular damage might be slight, what counted was the heart muscle which needed protection while the process was active; that Johnny would have to stay in bed until there were no signs of activity and that when he returned to school he would still have to be careful. He added: "I guess there'll be no basketball this year." His mother knew that would be the greatest blow of all but she counted on the boy's common sense and coöperative spirit.

This story has a happy ending. The boy made a good recovery. But you can see he was fortunate. He had a careful doctor, an intelligent and understanding mother and he himself was sufficiently alert so that his energies could be diverted into channels other than basketball and wrestling. Partly through the interest which the electrocardiogram had awakened in him he set to work to assemble quite a respectable radio.

If we vary any of the ingredients of this story we might have quite a different situation on our hands. A less biddable youth than Johnny, for example, a somewhat unruly, defiant, rowdy adolescent at loggerheads with his parents may present a trying therapeutic challenge. This is especially true if the child feels the restrictions of his illness to be a kind of punishment or if the parents ease their own concern and hostility by exploiting the situation and threatening the child. Even trained nurses have been known to say to such children: "If you don't keep quiet the doctor says you're liable to drop dead of heart failure."

From a psychological point of view there are two principal problems to deal with: One is in the patient, the other is in his parents. The chief problem in the child is to prevent boredom and to still the restlessness which so quickly overtakes him when he is deprived of his accustomed bodily activities, and finally to teach him what he can and cannot do, depending on the amount of cardiac damage. Early in his illness the child can be lifted from his bed into a comfortable steamer chair. Such a change in posture puts no extra strain on his heart, but on the other hand, may improve his morale greatly.

Soon after the acute toxic symptoms have subsided the services of a visiting teacher are essential. The longer the child is sick the more necessary this becomes—not so much to prevent loss of schooling as to pro-

vide some interest and substitutive activity and to prevent his slipping into a regressed, withdrawn state in which his chief satisfactions are in day dreaming. If lessons can be combined with, or supplemented by, interesting occupational therapy so much the better.

The problem of the parent is the more difficult to deal with and the more important. The bugaboo of rheumatic fever is the ever-present danger of recurring attacks with further damage to the heart. It is difficult to instruct a mother to be on the lookout for vague symptoms of reinfection, which are the common ones in childhood, without arousing undue anxiety in her and eventually by contagion, in her child. If we do arouse too much anxiety then she will over-protect her child, worry over him, fuss over him, keep him in bed long hours, urge him to eat and be alarmed at the slightest headache or evidence of fatigue. Your own imagination or experience can describe how a spirited child or a complaint one will react to such treatment. Or again, an over-anxious mother may, because of her fear, be blind to fairly obvious signs of trouble and assume a casual attitude which may be even more damaging than the over-solicitous one.

I have no magic formula to apply to this puzzling problem. But this much I can say: If the doctor aims to provide an atmosphere in which recovery from the first attack is facilitated and recurrences are to be prevented, then he must address himself to the concerns, to the worries and to the emotions of the mother. It is probably almost as important to listen to her as it is to listen to the patient's heart.

Although I have emphasized the place of the child's mother in all of this, the attitude of physicians, of nurses and attendants—whether in a hospital, an out-patient department or a cardiac home, is often of determining importance. If the child is to recover from the body blow that nature has dealt him and is to regain a place in his world, no matter how handicapped, then he must be taught the two most difficult lessons of childhood, if not of life: one is to defer an immediate satisfaction for an ultimate gain; the other is to accept certain inexorable limitations of his capacities. He will learn these lessons best if those responsible for him are themselves not over-burdened with anxiety. We should not, of course, fail to recognize the anxieties that the child himself is coping with. These may be mobilized and aggravated by the illness—though by no means solely caused by it.

Throughout this paper you will hear the word "anxiety" frequently

used. It is the most important psychological manifestation in cardiac patients. In the group I have just discussed, anxiety is more to be reckoned with in the parent than in the sick person. In the next group—sufferers from what are called cardiac neuroses—anxiety is of cardinal importance in the patient himself and in the formation of his symptoms. The term "cardiac neurosis" is a loose one. It is a diagnostic catch-all to define those patients who have unpleasant, often frightening, sensations which they attribute to their hearts or, again, who exhibit what we like to call functional disturbances of their hearts, such as tachycardia, palpitations and even sometimes extra systoles.

When a consultant examines such a patient and uses the most modern scientific equipment and after great care can find no evidence of structural damage to the cardiovascular system then the patient, if he has the temerity and extravagance to cling to his symptoms, is said to be suffering from a "cardiac neurosis."

Within the past few years it has become increasingly customary to send such a patient to a psychiatrist. When he arrives (let us call him Jones) the first thing he will talk about is the fact that he is in a psychiatrist's office. He's a bit shame-faced about that. He says he's never done such a thing before—as if he had been caught stealing money from his grandmother. This is an old story to the psychiatrist who soon puts his patient at ease. The next thing that comes up is the fact that Jones thinks the doctor thinks all of his symptoms are imaginary, otherwise he wouldn't have been sent to see a psychiatrist. This too is disposed of by the psychiatrist's reassuring and sympathetic attention. He explains to Jones that no symptoms are imaginary—if they are actually experienced—and that no one ever suspected him of malingering. The rest of the hour then is spent on a list of complaints and symptoms.

The psychiatrist pays close attention to the way in which the patient tells his story. He doesn't ask him too many questions in the first visit. What he is trying to do is to make a diagnosis—a psychiatric diagnosis, because on that will depend the choice of treatment and, in part, the prognosis.

Let us examine very briefly a few Joneses. Jones I is a man in the early fifties. For the last few days he has felt strangely apprehensive. He is tremulous and his hands are cold and moist. He says he has been having dizzy spells. On closer inquiry he does not actually experience vertigo, but momentary states of confusion with feelings of breathless-

ness and oppression in the region of the diaphragm. He has had difficulties before for which he has consulted a neurologist and he is accustomed to a certain degree of tension and apprehensiveness. This time, however, they are much more intense and disturbing. He feels panicky and convinced that there is something seriously wrong with his heart.

What happened was this: A year ago he was examined by his company physician, an excellent and well-trained young internist. This internist noticed in the electrocardiogram evidence of a wide S bundle branch block that had been present over a period of two years, according to previous electrocardiographic evidence. He said nothing to the patient about it, assuring him that everything was normal. A year later a new company physician re-examined him and told him there was something unusual in his E.K.G. This disturbed the patient greatly and since the two company doctors had not agreed he consulted a cardiologist. The cardiologist examined him carefully and made light of the finding, explaining it to him (at least so the patient told me), as a "slight surge of the S wave." This, of course, meant nothing to the patient and, let me add, it meant equally little to me. The only difference was, it was the patient's heart and not mine, so it didn't frighten me as it did him. I inquired as to the real meaning of the electrocardiographic changes and then took great pains to explain things to the patient and to reassure him. He was much relieved to discover that he was suffering only from his old familiar neurotic difficulties and he was able then and there to give up his heart disease. This was a gratifying, if superficial, result. The man leads an active, useful and full life and there seemed at that time no justification for exploring further into his emotional problems. It is, as you well know, by no means always so easy to lay a cardiac ghost as it was in this case of anxiety neurosis.

Take Jones II, for example. He is 30 years old, an extremely intelligent statistician. He was sent to me by an excellent cardiologist because the patient could not be convinced that there was nothing seriously wrong with his heart. He complained of palpitations at night. He would awaken with his heart pounding. He had vague pains throughout his chest. He said that at college he got too much exercise and had "sprung his heart." He said he was conscious of his "heart beating all around the bush." He said: "I was scared into a perfect jelly and thought of taking up religion to die a good Christian death." He was told not to dance and he began to be very careful of his health. He had many other bodily

preoccupations and spent hours every day brooding over his aches and pains and over his damaged heart. He had a bizarre and extravagant way of describing his feelings. He compared himself to "an old tooth waiting to be filled," and said that he "felt as if his heart were rotting."

The manner in which he presented his complaints, the semi-jesting, jocular, inappropriate affect which accompanied his bizarre and disturbing thoughts, as well as his fixed hypochondriacal preoccupations, convinced me that this was a seriously disturbed man with certain features to his make up characteristic of schizophrenia. This diagnosis was supported by psychological tests made by another examiner who described the patient accurately as an "intellectually compensated latent schizophrenic."

In a patient of this sort there is no use in attempting to approach the cardiac complaint directly. It has all the fixity and stubbornness of certain paranoid delusions. One can reassure him from time to time but reassurances do not stick. The wisest course is to disregard the symptoms and to address ourselves to the whole life-situation and to try to keep the patient in contact with others and with reality. This man had a brilliant military record, achieving high rank. His gifted scientific mind was put to excellent use. He even achieved a marriage of sorts but it was not distinguished by any deep feeling.

Jones III presents quite a different picture: a different diagnosis, different treatment and a different outlook. In November, 1945, I received a letter from Dr. Blank who wrote: "I am referring Mr. L.W.K. to you for your valued opinion and care. He is a high strung man with hypochondriacal symptoms and a labile hypertension." There was enclosed in the letter an abstract of the history and physical findings. The important facts were these: He was 36 years old; his blood pressure, in the right arm, was 180/100, in the right leg, 190/105. The patient had been hospitalized and given intravenous sodium amyta. After injection his blood pressure fell to 140/82. The heart was apparently normal and renal functional tests were within normal limits. An intravenous pyelogram showed slight distention of the kidney pelvis. The diagnosis was "Essential hypertension with a very prominent nervous factor in its origin."

This patient came willingly for psychiatric help. He was very much frightened—frightened that he would be permanently invalidated because of his hypertension. He saw himself in a wheel-chair after a

stroke. He feared a sudden heart attack, or that he might have to undergo a sympathectomy. He had many of the symptoms common in hypertensives: headache, buzzing in the ears, occasional precordial oppression and heaviness in the left arm. Further inquiry revealed a long history of neurotic complaints. He said of himself that he had always been overconcerned with his health. For a long time his gastrointestinal tract was the chief focus of his discomfort and concern but his anxiety had now attached itself to his blood pressure.

In spite of his disabilities he was an able and effective young business executive. His father too suffered from hypertension. I concluded that everything should be done to prevent this man's still labile blood pressure from becoming fixed at a high level. After further preliminary psychological studies I recommended psychoanalysis.

Two years after receiving the letter from the referring physician I wrote him the following letter:

Mr. L.W.K. had his last session with me on November 6th. As you know, he has had to be away a good deal on business trips. He has just returned from one to the West without his usual emotional and physiological upsets. This trip required his making several speeches which he was able to do without stage fright or cold sweats. His family doctor took his blood pressure about two weeks ago and found it to be 120/70. I think he has finally abandoned a conviction that he has hypertension, but he is still very gun shy of the blood pressure cuff. I imagine that he always will be.

You will be interested to know that he saw me 135 times for approximately 50 minutes at each visit."

Let me review with you briefly what transpired during the psychoanalytical treatment. As is usual in such treatment, one begins with the immediate and disturbing facts of the patient's life—the ones which he naturally first chooses to talk about. In this case it was his health and his worries over his future and the support of his family. What would happen to them if he should become permanently invalided? Gradually we penetrated behind this outer coating of defense and found in him a frightened, puny, pimply youth whose father had walked out on his mother. His father had had terrible rages and yet he was to him the ideal of a strong and heroic figure whom he remembered as an officer in World War I. But he never came back to them. The boy was left alone with an adoring, but bitter and unhappy, mother.

They lived in a part of the States where to be divorced was a permanent disgrace for a woman. The patient felt this keenly, became prematurely ambitious and self-reliant. He led his class at school but remained physically weak. He looked admiringly and enviously at the football stalwarts. This notion of weakness clung to him and in spite of more than usual success in his professional and domestic life it seemed to load the dice against him. Behind his driving ambition, there was great insecurity, great lack of self-confidence. What he actually wanted was failure and illness and to be taken care of. It was the old story of an unconscious wish being experienced as a conscious fear. All this was revealed to the patient—not as an intellectual process—but as a personal experience through which he passed gradually, accompanied by many disturbing emotions, including rage. Although the end result seems favorable, time alone will tell whether what he gained will remain with him permanently.

I have presented this patient as another example of an anxiety neurosis. He resembles the first one—the man who was so frightened because of his S wave, and the second one who was afflicted with hypochondriacal preoccupations. And yet the treatment in all three was different and in each case was aimed at the life-situation and personality structure, rather than at the cardiovascular symptoms.

There are many patients who exhibit far less overt anxiety than these three did. For example, I have in mind a woman of 38 whose history was one of tachycardia for a period of about 15 years. Her basic heart rate was usually 130-140 per minute, at times reaching a level of over 200. At other times, however, her rate dropped to 90 or even 80 to the minute. She had consulted a great many doctors (some very distinguished ones) and her list of medicines included atropine, digitalis, mecholyl, phenobarbital and quinidine. She had also had pressure exerted on her eyeballs, vagi and carotid sinuses, all without relief. And yet the heart was perfectly normal to examination. Nothing was ever found but paroxysmal auricular tachycardia.

She was repeatedly advised to have a psychiatric consultation. She admitted having had a "nervous breakdown" before the trouble began, but she said that she was quite able to analyze her own emotional difficulties and she saw no necessity whatever for psychotherapy. She had rejected all conceivable reasons for being nervous or tense.

In a patient of this sort it is sometimes impossible to proceed

psychiatrically. The whole emotional conflict is in a sense acted out by the heart. This is a true organ neurosis. Her unconscious drives are so threatening to her that they cannot reach the level of consciousness. They appear to find escape through a specific visceral disorder. And yet, psychological tests made on this patient showed a neurotic disturbance reaching serious proportions.

It would take us a little too far afield to discuss how we arrive at our diagnostic formulations in these patients. Among other things, we take into account their attitude toward the disorder, whether symptoms are diffuse or circumscribed, the type of sense organ that is involved and whether the symptoms are subjective only or observable by others (Levine²).

Usually in these so-called "cardiac neuroses" we have to differentiate between hypochondriasis, anxiety neuroses, and organ neuroses, and sometimes hysteria, in its technical, not its popular sense. None is necessarily exclusive of the other but the indications for treatment may depend upon the weighting of these various components. In all of them anxiety plays the predominant dynamic role. I will not attempt, in this paper, to define anxiety but to emphasize only that it is not entirely equivalent to fear and legitimate worry. It is a complicated emotional state in which hostility or rage as a defense against fear is also mobilized. There are unconscious elements in anxiety that explain why it is not always accessible to a rational common sense approach, why the accompanying cardiac symptoms of anxiety so often persist in spite of our best efforts at reassurance. In any case, we need to know what to reassure about.

The psychiatrist must make up his mind whether to explore and to uncover the deeper sources of anxiety or whether to help his patient cover them up and let healing occur by repression. The choice will depend upon the age, adaptability, intelligence and strength of character of the patient and on his capacity and willingness to relinquish symptoms.

In the older age groups, about which I will say a few words now, effective psychotherapy is by no means ruled out, but it is often difficult, especially in the presence of extensive cerebral arteriosclerosis. The group I have in mind are the sufferers from anginal attacks, from coronary insufficiency and infarction and from beginning symptoms of failure. Even though these patients have outspoken structural damage

to their hearts one must not conclude that emotional influences play no role in their illness or in their recovery.

Any experienced clinician can cull from his memory instances in which a profound emotional upset was followed by what we call a coronary accident.

A former President of the New York Heart Association recently told me of two such episodes in his clinical experience.³ The first concerned a man who heard the screeching of brakes and the crash of automobiles in front of his house. He dashed to the window only to see his own son's car in the wreck; whereupon he was seized with gripping substernal pain characteristic of a coronary occlusion.

The second story was about an elderly physician with hypertension. He began to complain of slight indigestion and, being somewhat hypochondriacal, he feared at once that he had a cancer of the stomach. But he did not seek medical advice. Instead he brooded over his illness and said to himself: "If I have lost weight, then I surely have a cancer." After days of torturous worry he finally summoned up enough courage to step upon the scales, but before it registered, he suffered a sudden coronary occlusion and died shortly thereafter.

Such histories could be multiplied out of your experiences I am sure. Perhaps it is wise to draw no etiological inferences from them—to recognize them as remarkable coincidences and to realize that coincidences are themselves facts of nature which merit study. We do know that outbursts of rage or startle-reactions, as from fright or the hearing of bad news, are sometimes followed by sudden cardiac deaths.

We have less information about the influence of prolonged anxiety or states of tension on the coronary circulation. On this matter our suspicions are not yet based on proven physiological observations. Inferences may, however, be drawn from illuminating observations, many of them emanating from Harold Wolff's laboratory, on the peripheral and visceral circulation.⁴ The vascular supply to the mucous membrane of the stomach (and also of the nose) alters with the emotional state of the subject; rage appears to be accompanied by engorgement of the lining of the stomach and sudden fear by blanching. Analogous changes occur in the bladder, the vagina and the large bowel. From Mittelmann's⁵ experiments we have learned that finger temperature may drop as many as 25° F. when the subject is in a state of anxiety. And again, Homer Smith's⁶ studies have demonstrated a reduction in

renal blood flow up to 40 per cent under similar conditions.

The two original experiments of Homer Smith have been corroborated and extended by Pfeiffer,⁷ working in Wolff's laboratory. In eighteen patients suffering from arterial hypertension rises in both systolic and diastolic pressures were observed when relevant life-situations were touched upon in interviews with them. Accompanying these rises in pressure there was a renal vasoconstriction reflected by decreases in the renal plasma flow up to 25 per cent of the control levels. This sometimes outlasted the rise in systemic blood pressure. In some cases the peripheral resistance to renal blood flow increased by as much as 40 per cent. Wolff and Pfeiffer conclude that the kidney in persons with arterial hypertension exhibits an abnormal vascular pattern characterized by increased arteriolar tone which is further increased by threats or assaults to the organism—physical or psychological. Such vasoconstriction, if prolonged, may damage the kidney parenchyma and eventually the brain and the heart. These conclusions support the theoretical ones proposed by others and myself in a monograph on the personality in arterial hypertension.⁸

Finally, let me add, that there is evidence in the literature that cardiac pain occurring under circumstances of emotional stress is associated with electrocardiographic changes.⁹ Artificially produced extra cardiac pain may be associated with similar changes.¹⁰ Whether these are the result of a diminished blood supply to the heart muscle because of vasoconstriction or are due to an extra demand for oxygen because of increased work is not yet clear.

Aside from considerations of etiology, however, sound therapy will have to take into account the patient's emotional state. There are some for whom prolonged bed rest acts as an irritant and whom sedatives will not quiet unless they are given adequate psychotherapy. According to recent observations made on Dr. Wortis' service at Bellevue, similar preparation is necessary in some patients before digitalis can be effective.¹¹

It is my impression that almost every one who suffers an infarction goes through a period of depression, sometimes quite severe. It may long outlast electrocardiographic evidences of damage to the heart and may delay restoration to even moderate functioning. But these depressed states usually yield in time to the faithful ministrations of the physician and especially to a regime of gradually increasing activity. They do not often require the special services of a psychiatrist. There

is no better psychotherapy for the cardiac invalid than to be permitted and encouraged to exercise when such advice is compatible with his cardiac reserve.

The heart and the precordial area are quickly responsive to emotional stimuli and, reciprocally, sensations coming from these structures are often felt and interpreted as emotions. The Greeks, you will recall, looked upon the midriff as the seat of the soul and not only as an aphrodisiac to which one applies suntan oil.

Perhaps the poets could write for us a real treatise on the irregularities of the heart—that extraordinarily acrobatic and versatile organ which leaps and bounds and jumps and turns over and sinks and rises and catches fire and freezes and is light as a feather or as heavy as lead. Finally it stops, and that is what we are all afraid of.

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THE ROLE OF SODIUM CHLORIDE IN THE MECHANISM AND TREATMENT OF CONGESTIVE HEART FAILURE*

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IT IS a truism that the processes of disease result to a large extent in only quantitative variations from the normal physiological equilibria. In this sense, the response of patients with congestive heart failure to addition or subtraction of salt from the diet is merely an exaggeration of the reaction in the normal subject. In 1904 Widal and Javal¹ described a diuresis, an excretion of 10 to 12 grams of salt and loss of weight of about 1.75 Kg within 2 or 3 days of instituting a low salt diet in normal subjects; and, conversely, an oliguria, retention of salt and return to the control weight on adding 10 or 15 grams of salt to the low salt diet. Recent refinements of these experiments by Lyons et al.² have demonstrated, in addition, significant downward or upward changes in plasma volume, venous pressure and extracellular fluid volume. Similarly, Grant and Reischsman³ have produced latent edema and plethora for a few days in normal subjects by adding 20-30 grams of salt to a normal diet.

It is my purpose to consider some of the reasons for the quantitative difference in response to salt in congestive failure, with special emphasis on renal factors. The clinical experiments which I shall present are the work of my associates, R. Mokotoff, R. E. Weston, D. J. W. Escher, L. Hellman, M. Cherkasky and G. Ross and their technical, dietetic and nursing assistants. My own role has been purely one of a trophic and regulatory center, sensitive, I hope, to stimuli from the periphery.

Since the beginning of this century, it has been known that there are two major components in the mechanism of edema, whether of renal or cardiac origin. From Starling's⁴ experiments, the dynamic bal-

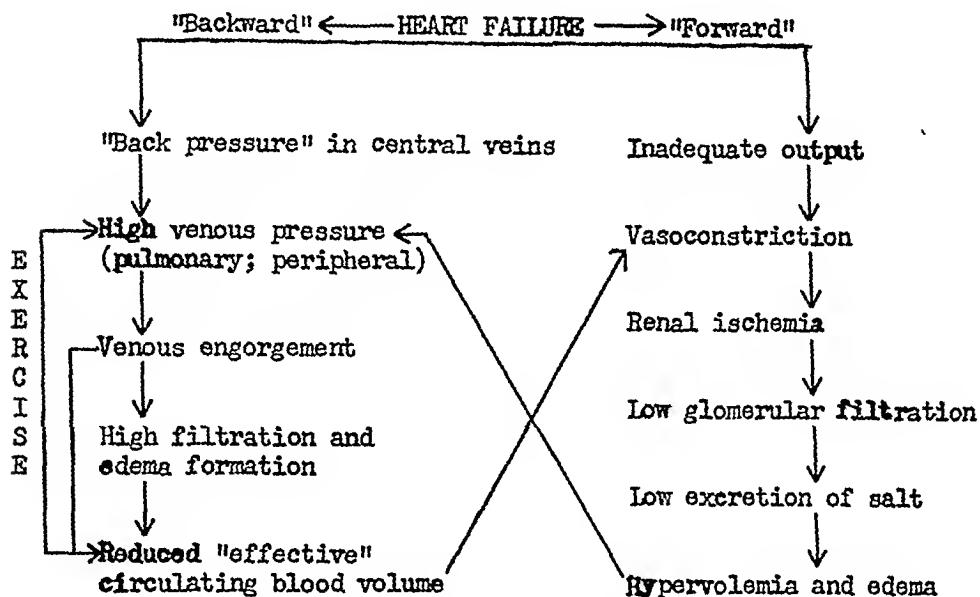
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ance of physical factors in the filtration and reabsorption of fluid in the capillaries was clearly established. From Widal's⁵ clinical studies, there was no doubt that retention of salt by the kidney was directly responsible for the degree of edema and gain in weight of nephritic patients. However, no simple combination of these two processes—the one, pre-renal regulation of fluid exchange, and the other, renal excretion of sodium chloride and water—was integrated into the mechanism of cardiac edema, a basic feature of congestive heart failure. In fact, clinicians and their physiological colleagues soon became entangled in the foamy webs of colloid chemistry and the convenient mysteries of permeability, and succeeded in persuading themselves and others that the kidneys had little or nothing to do with renal or nephrotic edema and certainly little to do with cardiac edema. The major edemas were pre-renally predestined and the renal component was largely a secondary matter of preserving a normal plasma electrolyte composition.

It was not realized for a long time that urinary output of salt alone could not be used as a measure of the causal relation of renal function to edema for the simple reason that there is a complex division of labor within the kidney itself which can influence the over-all figures enormously. For this job analysis of the kidney we are largely indebted to the ingenuity and industry of Homer W. Smith^{6, 7} and his disciples. As a result of their far-reaching studies it is now apparent that the process of renal salt excretion must be dissected on a systematic basis to determine 1) the renal blood flow; 2) the amount of salt and water filtered in the glomeruli, which is the load presented to the proximal renal tubule, where the major or obligatory reabsorption of salt and water occurs; and 3) the residual load of salt and water presented for reabsorption to the distal renal tubule, where the final adjustments are made in the composition of the urine. When one considers that there are definite quantitative relationships between these kidney functions, that they are under the control of intrinsic renal and extrinsic nervous and hormonal factors, and that one of the chief functions of the human kidney is the conservation of base and water, necessitated by the enormous filtration of these substances in 24 hours, it becomes evident that no conclusion can be drawn regarding the role of renal salt excretion in the mechanism of congestive heart failure without careful quantitative study of renal hemodynamics in this condition. This approach was first made by Seymour et al.,⁸ Warren and Stead,⁹ Merrill,¹⁰ Lauson, Bradley and

CHART I



Cournand¹¹ in their basic studies of cardiorenal interrelations in chronic congestive heart failure and acute shock.

I suppose it is not necessary to define congestive heart failure before this audience. Nor, I hope, will you take issue with me on the statement that when the heart becomes inefficient and fails it is like the old Roman god, Janus, facing both ways—forward and backward (Chart 1). The signs and symptoms of backward failure are more obvious, more striking, more readily measured clinically in terms of venous pressure, size of liver, pulmonary rales and edema; the signs and symptoms of forward failure, with the exception of acute peripheral circulatory collapse, are more subtle and difficult to measure because we are dealing with cardiac output and blood flow to various organs. As D. W. Richards¹² has aptly commented, in backward failure there is still forward flow but with back pressure in the lungs or systemic veins. That this increased pressure is partly compensatory and actually maintains cardiac output at a higher level than it would otherwise reach was early appreciated by Starr¹³ and McMichael.¹⁴ However, regardless of whether the cardiac output is low, normal or high in the presence of elevated venous pressure in congestive failure, it can safely be assumed that, prior to failure, that same heart was capable of a higher output because it was

TABLE I. RENAL HEMODYNAMICS IN CONGESTIVE HEART FAILURE
(Data from R. Mokotoff et al.)

Subject	Renal Plasma Flow	Glomerular Filtration	Filtration Fraction
	cc. per min	cc. per min	per cent
Congestive Failure	191.5±41.9	66.8±10.9	37.8±7.0
Control	627±74.5	103±10.0	16.6±1.5

more efficient. To put it another way, if a more normal heart were suddenly introduced into the circuit its output would be much higher than that of the insufficient heart even in high output failure. We can safely conclude that in congestive failure the output of the heart is inadequate for the body's requirements even at rest, and certainly during exercise or any other condition that increases metabolism and the load on the heart.

Heart failure is a form of circulatory stress. It is well to remember that whenever the circulation is exposed to stress, whether from sudden large hemorrhage, loss of circulating plasma into a traumatized area, or other types of shock or dehydration, all associated with an inadequate cardiac output, a redistribution of available blood flow occurs whereby the more vital organs are supplied at the expense of blood flow to skin, muscles, gastro-intestinal tract and kidneys.^{15, 16, 17} Marked reduction of renal blood flow and glomerular filtration develops in these situations of acute stress. It is significant, therefore, that Merrill¹⁰ and later Mokotoff¹⁸ have shown these changes (Table I) to be regularly present in chronic congestive failure, regardless of the level of venous pressure or the temporary absence of edema as the result of treatment; but somehow an expression of an inadequate cardiac output relative to the body's requirement.

This markedly reduced renal blood flow is not simply the sequel of renal venous congestion, because it occurs even with only slight elevation in venous pressure. Furthermore, as the Bradleys¹⁹ have shown in normal subjects, it takes a pressure of 14 to 22 mm. Hg in the renal vein—about 3 times the normal level—to produce a 25 per cent decrease in renal blood flow. Compare this with reductions of 50 to 80 per cent in renal blood flow in nearly all patients with congestive failure. A more striking difference between forward ischemia and backward con-

gestion in the kidney is seen in the glomerular filtration fraction. The Bradleys in their abdominal pressure experiments, found a proportional reduction in renal blood flow and glomerular filtration—hence, an unchanged filtration fraction. However, their experimental procedure not only increased post-glomerular resistance but also increased renal intrapelvic pressure, which could explain this deviation from the expected result. On the other hand, in congestive failure the glomerular filtration is never reduced as much as the renal blood flow; hence, the filtration fraction reaches abnormally high levels, an excellent compensation if you so wish to interpret it. Naturally, in a patient who has a high venous pressure and a tight abdomen full of ascitic fluid, the resulting renal venous congestion will add a further hindrance to the diminished renal inflow of blood and bring about a greater reduction in glomerular filtration of salt, beside producing a more severe oliguria. The dramatic improvement after abdominal paracentesis may well be the result of relief of renal venous congestion in such cases.

One of the important implications of reduced renal blood flow and glomerular filtration in patients with heart failure is the effect of exercise. The renal function measurements are usually made on patients at bed rest and under basal conditions. They are, therefore, probably maximal values since, as Merrill and Cargill²⁰ have shown, light exercise or ambulation regularly reduces renal blood flow by diversion of blood to muscles, and, in congestive failure, lowers glomerular filtration further. Also, exercise increases the venous pressure for relatively long periods in the cardiac patient, comparable with the findings of Landis et al.²¹ that exercise increased central venous pressures in dogs with auricular fibrillation or ligation of a coronary artery. Therefore, just as in subjects with hunger edema, described by Denz,²² the tendency to persistence or recurrence of edema will be much aggravated in the cardiac who is up and around. He will filter more fluid into his lower limbs and at the same time have a reduced urinary output of salt for which his kidneys may not be able to compensate during the hours of rest. The stage is therefore set for an attack of nocturnal pulmonary congestion since the failing heart cannot respond to the increased circulating volume during recumbency by adequate increase of cardiac output. The result is elevation of pulmonary arterial and capillary pressures. Other factors, of central nervous origin, are also involved in these attacks.

Another important point in renal hemodynamics has occasioned various interpretations and some misunderstanding. This concerns the role of reduced glomerular filtration in the retention of salt in congestive failure. It has been argued that the amount of salt excreted daily by the normal person is so tiny a fraction of the amount filtered that even a 50 per cent reduction of filtration should make little difference when one considers that a minute change in tubular reabsorption could compensate for it. Therefore, there has been a tendency for some investigators to disregard the lowered glomerular filtration in congestive failure, and, instead, to emphasize the possibility of increased tubular reabsorption of water and salt, presumably the effect of increased anti-diuretic hormone and other hormones. Much has been made of the lack of exact correspondence between the degree of reduction of glomerular filtration and the output of salt.²³ In all this type of argument it is sometimes forgotten that one of the chief functions of the mammalian kidney is conservation of salt. For this reason, as Homer W. Smith²⁴ has pointed out, the filtration rate becomes very important precisely because only a small fraction of filtered saline is marked for possible rejection. Therefore, salt is dealt with as a threshold substance, like glucose, but in a peculiarly different manner. Instead of having a maximum tubular reabsorption of so many milligrams per minute as in the case of glucose, there is probably only a maximum reabsorption, by the proximal convoluted tubule, of a certain amount of sodium for every 100 cc. of glomerular filtrate. This, of course, is necessary to maintain the isotonic concentration of sodium in the plasma and relates sodium to water reabsorption. However, the volume of glomerular filtrate which can be dealt with by the tubule in this manner is relatively unlimited, as shown by Pitts²⁵ and Lotspeich²⁶ for chloride and bicarbonate ions, the chief partners of sodium in the extracellular fluids. The kidney is therefore set primarily to regulate the concentration of salt in the body fluids and is relatively insensitive to the volume of extracellular fluids as long as they are isotonic. This evolutionary habit of the kidney is a major obstacle in the management of edema.

When glomerular filtration is reduced, the load of saline for the proximal tubule is correspondingly diminished and, finally, the distal tubule is presented with so little salt as to fall well below its maximal reabsorptive capacity, since only about 15 per cent of the glomerular filtrate normally reaches the distal tubule. Here water and salt reabsorp-

tion can be widely dissociated, thanks to the action of anti-diuretic and perhaps other hormones and acid-base regulation. The smaller load of salt may be practically entirely reabsorbed as part of the normal conserving activity of the distal tubule. The result is salt retention in the body and all the consequences that flow from it. You can see, however, that the initial and determining factor in this sequence is reduction of glomerular filtration, with upset of the normal glomerulo-proximal and proximal-distal tubular balances.

To use simple terminology from the economic sphere, we might consider glomerular filtration as a supply bureau for essential saline, of which normally 98 to 99 per cent is returned via the tubules for the domestic or internal economy while 1 or 2 per cent is routed for export into the urine. The distal tubule is the export control bureau. If supply or filtration of saline is excessive, because of brisk import of raw materials, ingested salt and water, export volume rises rapidly both in absolute units and as percentage of total filtration as a new equilibrium is established, with a somewhat increased internal supply. However, if glomerular supply or filtration falls toward the minimum required for the body's economy, as in extrarenal loss of body fluids or salt privation, export is not simply reduced proportionately but is largely or entirely cut off, as it should be in the interests of the internal economy. Unfortunately, in cardiac failure, when internal transportation becomes congested and is rerouted, the glomerular supply bureau receives less than the normal quota of saline although production of saline continues because of unrestricted import of raw materials. The proximal tubule being devoid of intelligence necessarily passes on a much smaller amount for export in spite of the fact that extracellular warehouses may be filled to the bursting point. The distal tubule, receiving a lesser volume of saline, reabsorbs nearly all of it. There apparently is no way by which the glomeruli or the tubules can be informed of the peripheral congestion and edema except by improving transport.

What is to be done under these circumstances? First, the external supply or import of raw materials, sodium and chloride, should be sharply reduced to prevent further accumulation of the finished product in the body; second, drastic measures must be taken to improve transport on the one hand and to relax export controls on the other. An intelligent physician will attempt to change the internal economy and to regulate the import of salt somewhat against the established habits or

individual liberties of the patient. The sooner this happens, the better.

Let us return to the evidence for the theory that the renal tubules are functioning normally in regard to salt in congestive failure. In our laboratory, Mokotoff et al.¹⁸ have shown that the tubular reabsorption of sodium is set at the same constant level of 133 meq/liter of glomerular filtrate in the cardiac as in the normal subject on the same diet. This level is not affected by artificial increases in glomerular filtration. This figure, however, should not be taken too literally in estimating daily urinary excretion of sodium because it was determined with mannitol clearance as a measure of glomerular filtration. Mannitol unfortunately is an osmotic diuretic; therefore, it prevents the normal reabsorption of sodium somewhat and causes more salt to appear in the urine even in the cardiac patient with failure. Furthermore, slight changes in tubular reabsorption of sodium which might have a considerable bearing on the mechanism of cardiac edema would be very difficult to detect by the clearance methods. Whether studies with radioactive sodium will be more accurate in this respect has not yet been established. For the time being, it is a fair working hypothesis that the renal tubules are behaving normally in cardiac failure, that they are not under unusual hormonal influences, and that they respond in the usual manner to increases or decreases of the amount of filtrate and its content of sodium chloride.

An important question must be answered—what is the mechanism of the renal ischemia in congestive failure? Mokotoff and Ross²⁷ have investigated this problem. There are two possibilities—neurogenic or humoral. Using high spinal anesthesia to block autonomic reflexes and ephedrine to prevent fall in blood pressure, Mokotoff and Ross have found no significant changes in renal blood flow or glomerular filtration rate in patients with chronic congestive failure. These results would seem to exclude a neurogenic basis for the renal vasoconstriction. Merrill¹⁰ has demonstrated the presence of renin in renal venous blood of cardiac patients in chronic failure. Whether this speaks for cause or effect of renal ischemia cannot be decided now. Other possibilities, such as Shorr and Zweifach's²⁸ VEM are being considered in searching for a humoral mechanism of renal origin. So far as the renal efferent constriction and the resulting high filtration fraction are concerned, they may stem from an intrinsic renal compensatory mechanism to counteract the effect of decreased blood flow on glomerular filtration pressure and filtration rate.

TABLE II. EFFECT OF ADRENOCORTICOTROPHIC HORMONE (ACTH)
ON RENAL HEMODYNAMICS IN HYPOPIGMENTARISM
(Data from L. Hellman et al.)

Subject	Period	Renal Plasma Flow	Glomerular Filtration	Filtration Fraction
cc. per min. per 1.73M ² per cent				
F. S. (Male)	Control	362.5	58.9	16
I. S. (Female)	ACTH	599.0	100.0	16
	Control	483.0	80.2	16
	ACTH	784.0	125.7	16

To broaden the subject of possible mechanisms in control of salt excretion in heart failure, my colleagues Hellman, Weston and Escher²⁹ have approached the question of renal function from the endocrine aspects as distinct from the cardiodynamic viewpoint. It has been well established by the clinical studies in Addison's disease by Talbott et al., Waterhouse and Keutmann,³¹ and by experiments on hypophysectomized or adrenalectomized dogs by White and his associates,^{32, 33} that intact adrenal cortical function is essential not only for normal renal tubular activity but also for adequate renal blood flow and glomerular filtration. Since the adrenocorticotrophic hormone is the intermediary between the central nervous system and the anterior pituitary on the one hand, and the adrenal cortex on the other, we have administered this hormone to patients with anterior hypopituitarism and low renal blood flow and filtration rate. A striking increase (57 to 70 per cent) was produced in both these functions, as expected (Table II). The implications in congestive heart failure have not been exploited as yet, but we are considering the role of malnutrition in anterior pituitary function. We realize that glomerular and tubular effects of adrenal cortical hormone release may counteract each other. Thus, increase in filtration would favor clearance or excretion of salt and water, other things being equal. However, increase in salt-retaining adrenal steroids would enhance tubular reabsorption of salt. Just what happens in congestive heart failure under different experimental conditions must be the subject of further study.

When we think of the liver in connection with salt retention in

cardiac edema, two major possibilities arise—1) portal venous hypertension aggravating the effects of systemic venous congestion, especially in patients with long standing cardiac failure and enlargement of liver; 2) deficient inactivation of salt and water retaining hormones by a poorly nourished, congested, fatty or centrally necrotic liver. There are some facts available on portal hypertension; on the question of hormone inactivation, we are dealing largely with hypothesis and assumption. In extenuation it should be said that it is extremely difficult so to control conditions clinically or experimentally as to obtain clear proof of diminished inactivation of pituitary or steroid hormones by the liver in heart failure. Nor is it certain whether the increased antidiuretic substance excreted in the urine of patients with cirrhosis, as described by Ralli et al.,³⁴ is a primary or secondary event in relation to ascites and edema.

The discussion up to this point has indicated the central role of the kidneys in the mechanism of chronic congestive heart failure, or at least, of its most obvious signs, venous congestion and edema. We have seen that various hemodynamic and perhaps hormonal influences conspire to decrease the excretion of salt by the kidneys, which are innocent victims of the underlying circulatory disturbance. The diversion of blood from the ample renal blood supply to other regions of the body apparently is as constant a phenomenon in chronic congestive failure as in acute shock of various etiologies. A humoral mechanism is apparently involved in this redistribution of blood in chronic heart failure. The degree of the reduction in renal blood flow and glomerular filtration is more modest in the chronic cardiac than in severe acute shock, but its ultimate effect on excretion of salt is much more significant because of the time element. However, everything seems to point to the view that the kidneys are behaving as a conserving mechanism for salt in congestive failure, just as in the normal state or in conditions of salt depletion, in spite of the fact that there often is a large excess of saline fluid in the plasma and elsewhere in the extracellular spaces. Injected hypertonic salt solution, as Futcher and Schroeder³⁵ demonstrated so clearly, is eliminated at a rate less than 30 per cent of the normal in severe congestive failure, with consequent increase of weight due to edema. Excess of water alone, as Newburgh,³⁶ Schemm,³⁷ Schroeder³⁸ and many others have shown, is dealt with as in the normal by increased, although delayed, diuresis.

What practical conclusions can be drawn from the preceding physiological data to aid us in the management of congestive heart failure? It is a truism that little or no salt solution can be formed or accumulate in the absence of salt in the diet, no matter how potent edema producing factors are. The only exception is uremia, when even water may be retained and edema fluid of very abnormal electrolyte constitution result. There is no disagreement among clinicians as to the importance of restricting salt in the diet; there is a difference of opinion as to the degree of restriction and the practicability of the process. There is no problem in regard to acute congestive failure—any plan involving bed rest, digitalization, mercurial diuretics³⁹ and reasonable limitation of salt will usually be effective. The patient is ordinarily in a mood to coöperate and the results of treatment are soon apparent.

The situation is entirely different in chronic congestive failure. Here we face years of invalidism, the need for continuous medical treatment, the effects of drugs, of passive congestion and of psychologic factors upon the appetite and nutritional state of the patient. On the part of the physician, there is the philosophy of treatment. Should one insist on the diet with a minimal sodium intake compatible with freedom from edema or pulmonary congestion, or should one adopt the plan of a freer diet with frequent mercurial injections to hold edema in check? The latter is much easier for the doctor; the former requires considerable education of the patient and at least some knowledge of low sodium diets on the part of the physician. The situation is not unlike the present conflict in the management of diabetics who require insulin, with the significant difference that excess salt stays in the body while excess sugar runs out.

Let us agree at once that the cardiac patient who on casual limitation of salt requires only one or two mercurials a month is not really the subject of this argument. Let us confine our attention to the ever-growing number of patients who are receiving from one to seven mercurials a week, who spend most of their days travelling to doctors' offices or to clinics, who are completely useless economically and who, sooner or later, lose more and more of their own weight and respond less and less to diuretics. We have seen many such patients at the Montefiore Hospital react very well to a balanced low sodium diet, containing about 1.5 to 2.0 grams of salt. We have trained a fair number of these patients to continue on the diet at home. We have made it easier

TABLE III. EFFECT OF LOW SALT AND RICE DIETS ON RENAL HEMODYNAMICS IN HYPERTENSIVE PATIENTS

(From data of R. E. Weston et al)

Subject	Diet	Renal	Glomerular	Filtration
		Plasma Flow	Filtration	Fraction
		cc. per min. per 1.73M ²	per cent	
G. B.	Full	393	104	27
	Low salt	372	88	24
	Rice	366	65	17
R. C.	Full	412	98	24
	Low salt	479	96	20
	Rice	364	66	18
	Full	491	101	21
A. M.	Full	223	54	24
	Low salt	238	37	16
	Rice	196	32	16
	Full	252	58	23

for them to take the most difficult hurdles in dietary management—the problem of bread and milk products. We have persuaded the nutrition department and our hospital administration to provide salt poor bread for distribution to out-patients. We have included sodium free milk ("Lonalac," Mead Johnson) in the diet, not to be taken unflavored as a drink, but to be used on cereals or in soups, custards, etc. Finally, we have made every effort to obviate the koshering or ritual salting of meat prior to cooking. The successful demonstration to even the mercury hardened patient that edema rapidly disappears and reaccumulates so slowly on our salt poor diet that only an occasional mercurial a month is necessary, has had a striking influence on the coöperation of the patient. Some have been restored to gainful occupation, most have been more comfortable than on any previous regime. Some are, of course, ineducable, just as in the case of some individuals with diabetes, obesity or peptic ulcer.

What are the disadvantages of the low salt diet? First, there is the change in flavor of food in spite of the liberal use of other condiments.

This may be very serious in some instances of malnutrition because there is no good substitute for salt in taste. On our diet, the permission of the use of 1 or even 2 grams of salt from a shaker, daily, may make a great improvement in the palatability of the diet without exceeding the renal excretory limit in some patients. Second, it is still very difficult in many parts of this medical metropolis to purchase salt poor bread and other necessary items of the diet, such as unsalted canned vegetables. Very few hospitals bake their own salt poor bread. Crackers, cookies, rolls, cake and other variants of the bakery are taboo for the unfortunate cardiac. What a field for an enterprising bakery! Third, there is evidence to indicate that a very rigid salt poor diet in itself may cause a further reduction in glomerular filtration and renal blood flow, something the very opposite of our therapeutic goals. Thus Weston, Hellman and Escher⁴⁰ have found as much as a 40 per cent reduction of the glomerular filtration in hypertensives without heart failure, on very low sodium diets like the rice diet of Kempner,⁴¹ which, however, is also very low in protein (Table III). Mokotoff observed lesser changes on salt poor diets in normal subjects;¹⁸ Perera and Blood⁴² have recently reported similar results in uncomplicated hypertensives. It should be noted that these effects of low salt diets are not important in the usual case of congestive failure. However, they are of interest in the problem of so-called mercury-fastness or failure to respond to mercurial diuretics, a condition of importance in advanced stages of congestive failure. Let us examine this more closely.

It was stated earlier that the amount of salt excreted by the kidney involved a so-called threshold. Essentially, this means that the proximal and distal tubules separately exercise their reabsorptive capacities for sodium chloride and that what is allowed to escape into the final urine is simply the excess above these limits. This residual amount will be determined, therefore, by four factors—1) the serum sodium and chloride levels; 2) the glomerular filtration rate; 3) the maximal reabsorptive capacity of the proximal tubule; 4) the maximal reabsorptive capacity of the distal tubule.

Weston and Escher⁴³ have some evidence to show that the patient in severe congestive failure who is "mercury-fast" simply cannot filter enough salt to exceed the normal reabsorptive capacity of his tubules because of a combination of a low serum sodium and chloride level and a very low glomerular filtration rate. As a result, even the inhibiting

TABLE IV. EFFECT OF INCREASE IN GLOMERULAR FILTRATION ON
RESPONSE TO MERCUXANTHIN IN "MERCURY-FAST"
CARDIAC PATIENT

(From data of R. E. Weston and D. J. W. Escher)

<i>Subject</i>	<i>Period</i>	<i>Glomerular Filtration</i>	<i>Urine Volume</i>	<i>Serum Sodium</i>	<i>Filtered Sodium</i>	<i>Urine Sodium</i>
		<i>cc/min.</i>	<i>cc/min.</i>	<i>meq/l</i>	<i>meq/min.</i>	<i>meq/min.</i>
E. S.	Control	54.6	1.21	123.2	6.74	.002
	5 per cent NaCl	62.5	1.41	138.5	8.63	.004
	Mercuxanthin	83.5	12.50	135.2	11.30	1.222
		65.4	8.88	134.5	8.80	.725

action of mercury on tubular reabsorption fails to increase the urinary output of salt significantly. However, a sharp increase in glomerular filtration, produced by hypertonic saline or by aminophyllin, promptly converts the unresponsive to a responsive kidney (Table IV). The effect is temporary because of the difficulty of maintaining the increased filtration artificially without unpleasant side reactions.

Does one gain anything in edematous patients who happen to have low serum sodium and chloride, if one deliberately increases the salt intake in order to produce a better salt diuresis with mercury? The answer is "NO"! One may promote a higher excretion of salt during the mercurial diuresis, but the amount of administered salt is never eliminated entirely and the net result is a gain in the salt content of the body. As a matter of fact, the crux of this problem is the manner in which the extra salt is given. If it could be administered safely in very hypertonic form, and the fluid intake sharply restricted for some days to prevent formation of extra edema fluid, the resulting rise in serum sodium and chloride might ultimately alter the renal excretory pattern. Intravenous injection of hypertonic saline at the rate tolerated by patients in congestive failure seems to have little net effect on the urinary salt output in the absence of diuretic drugs. The data of Futcher and Schroeder³⁵ have clearly shown this, as well as the resultant increased edema in their cardiac patients.

What about the role of large quantities of fluid, as in the Schemm³⁷ regime, in the mobilization of edema? From the physiological experi-

ments of Wolf⁴⁴ on normal subjects on normal diets it is evident that the kidney cannot excrete urine with less than about 0.1 per cent of salt or 1 gram per liter. Gorham et al.⁴⁵ have applied this fact to edematous cardiac patients given a diet with only 2 grams of salt. They were able to double the small urinary output of sodium and reduce edema by raising the fluid intake from 1500 cc. to 3000 cc. or more. However, there was little difference in the total sodium excreted on 3000 cc. or 6000 cc. of fluids, probably because the kidney of the edematous cardiac can form urine with much less than 0.1 per cent of salt. Obviously, every extra gram of salt available in the diet will require one or more extra liters of fluid to be excreted, and under these circumstances the intake of fluid necessary to force loss of sodium from edema fluid over and above the sodium from the diet may easily reach 5 to 10 liters; amounts which, I am afraid, only thirsty Montanans could drink daily either orally or venously. Therefore, there is very little point to forcing fluids on the cardiac patient. There is also no reason for restriction of fluids. Perhaps we can agree on the elimination of the offending grams of salt from the diet by education rather than mercurialization.

As a final resort in the treatment of severe congestive failure when all the ordinary diuretic measures have proved inadequate, we suggest peritoneal dialysis with 5 per cent glucose solution in preference to frequent abdominal taps or the use of Southeby tubes. Cherkasky and Hellman⁴⁶ have shown this procedure to be very effective and not unnecessarily risky. It entails primary electrolyte depletion of 10 to 20 per cent followed by secondary water loss, with considerable net loss of edema. The extra amount of salt removed from the peritoneal cavity in this manner corresponds to the output during an excellent mercurial diuresis. Adequate dietary restriction of salt will then help to maintain the patient at the new weight level or to slow up the rate of reaccumulation of ascites and edema. Poor results will occur in patients with severe renal insufficiency or in the moribund stage of congestive failure.

In this discussion, the role of salt in the mechanism of congestive heart failure has been presented from the renal aspect, although with no intention of neglecting the well-known dynamic exchange of fluids between the circulating blood and the extravascular tissue fluids. Emphasis has been laid on the compensatory renal ischemia in heart failure and the unfortunate effect on glomerular filtration of salt. The peculiar division of labor within the kidney makes it inevitable that reduced

glomerular filtration will always lead to retention of salt, hence edema and congestion, as long as tubular reabsorption is normal or increased. For this reason, treatment of congestive failure requires restriction of dietary salt, improvement of renal circulation and filtration by more efficient heart action, however produced, and inhibition of tubular reabsorption by mercurials or other means. The problem of the mercury-fast patient has been analyzed. The basic indication in chronic heart failure is continued and adequate restriction of salt in the diet. This involves an educational program directed toward physicians, dietitians, nurses and social workers, as well as to patients and their families; and should include an efficient mechanism for the wide distribution of salt poor bread and other essential dietary aids. The New York Heart Association might profitably add this attainable objective to its fine community service program as a goal for the immediate future.

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RECENT ADVANCES IN THE FIELD OF CARDIOVASCULAR DISEASE*

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IN considering recent advances in any field, one must first decide what is included in the term "recent." Since this decision was left entirely to the speaker, it has been decided to include chiefly events since 1940. The list as originally compiled was a long one, and it would be quite impossible to consider in the available time all the topics that seemed deserving of inclusion. It should be clearly understood that this is not a review of the recent literature; it is, rather, a personal selection from a long list of subjects that seemed to lend themselves best to the purposes of these lectures. It is quite certain that other lists, as long and representative as the following, could be prepared without difficulty.

The topics chosen for consideration fall readily into two main groups:—those which deal with diagnosis, including increased knowledge of etiologic factors, and those which represent progress in the prevention and treatment of disease. They will be discussed in that order.

Catheterization of the heart: Congenital anomalies of the heart have received a great deal of attention in the past several years, largely because of the successful correction of several of these by surgical means. One of the important diagnostic methods applied to the study of such lesions has been catheterization of the right side of the heart; a technique introduced many years ago, but perfected and brought into general use through the work of Cournand and his associates.¹ As most of you know, a small catheter is introduced into a vein of the arm, or the femoral vein, and under fluoroscopic guidance is passed steadily upward until it enters successively the vena cava, right auricle, right ventricle, and pulmonary artery. Samples of blood may be with-

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drawn as desired from the great veins and the right side of the heart for determination of its oxygen content, and the pressure can also be determined at different levels. If the oxygen content is significantly higher than normal in the blood from the right auricle or ventricle, one immediately suspects a shunt from the left side of the heart through an interauricular or interventricular septal defect. Analysis of blood from the right pulmonary artery may reveal a higher oxygen content than that in the upper right ventricle, which would suggest the presence of a patent ductus arteriosus pouring arterial blood into the pulmonary artery. The tip of the catheter can often be passed through septal defects into the left auricle or ventricle, as shown by fluoroscopic determination of its position and by the withdrawal of pure arterial blood. The safety of the procedure is sufficiently indicated by the fact that thousands of patients have now been subjected to it without serious discomfort and without injury. It is undoubtedly an important addition to our diagnostic methods and a technique that may yield even more important information in future with respect to fundamental problems related to cardiac physiology, function, and failure.

Neurocirculatory Asthenia: One of the significant advances in diagnosis in recent years has been that in our understanding of the condition known variously as irritable heart, disordered action of the heart, soldiers' heart, vasomotor instability, cardiac neurosis, DaCosta's syndrome, effort syndrome, anxiety neurosis, and neurocirculatory asthenia. It is my impression that greater progress has been made toward an understanding of this complex and serious condition in the past six years than in all the preceding decades since DaCosta first described it in 1871. A number of careful and thoughtful studies have been published in England and the United States, and while many of them are commendable, one cannot avoid particular mention of the splendid papers by Paul Wood² in England and those by the distinguished group at the Massachusetts General Hospital,³ and by Friedman⁴ in this country. Inasmuch as Wood's was the first of this recent group of fine studies, it is perhaps appropriate to quote briefly from it in order to indicate the trend of recent thought upon this subject.

In discussing the etiology of the condition he remarks: "We have seen that the symptoms and signs of DaCosta's syndrome are produced by central stimulation; there remains to be considered the origin of

the central stimulation. It must be emphasized that the condition is as common in civilians as in soldiers, and that even when present in soldiers, it was present before enlistment more often than not. It is clear, however, that trauma, high explosives, wounds, and gas poisoning are relatively unimportant. The chief factors seem to be the family history, constitutional incapacity, infection, neurosis, and undue mental or physical strain."

A detailed study of one hundred unselected cases immediately revealed two things: first, that a factor in the majority of cases was a fear of and dislike for Army life, and second that a psychiatric diagnosis could almost always be made—depressive state, anxiety neurosis, hysteria, hypochondriasis, etc. To quote again: "The essential common factor was the emotional reaction. The special feature which distinguished the group from other psychoneurotic physical patterns was the establishment of a link between the emotional reaction and effort. This link was usually forged when emotional symptoms were misinterpreted and the heart blamed, so that fear of effort followed."

His summary and conclusion are stated as follows: "1) The symptoms and signs of DaCosta's syndrome more closely resemble those of emotion, especially fear, than those of effort in the normal subject. 2) The mechanism of the somatic manifestations depends upon central stimulation, not upon hypersensitivity of the peripheral autonomic gear. 3) This central stimulation is emotional, and is commonly the result of fear. 4) The reaction becomes linked to effort by a variety of devices, which include misinterpretation of emotional symptoms, certain vicious circular patterns, the growth of a conviction that the heart is to blame, consequent fear of sudden death on exertion, conditioning, and hysteria. 5) Incapacity tends to be exaggerated consciously or subconsciously in order to protect the individual from further painful emotional experience. 6) It is urged that the diagnosis of "effort syndrome" be dropped. A proper psychiatric diagnosis is nearly always available; if attention is to be called to the presence of effort intolerance, let effort intolerance be added in brackets."

In that same year, 1941, there appeared in British journals many other studies⁵ which while less extensive and conclusive than the one just quoted, are nevertheless important because the authors arrived independently at the same general conclusions, namely, that so-called effort syndrome is essentially of emotional origin and is closely related

to, if not identical with, anxiety neurosis. If we turn to our own country, we find that the Massachusetts General group have also arrived at practically the same conclusion, on the basis of extensive observations. Those of you who have read their fine series of reports, still incomplete, will recall that all recent papers have contained in the title the three terms "neurocirculatory asthenia, effort syndrome, or anxiety neurosis," used synonymously.

Friedman,⁴ in a series of interesting studies, has also obtained apparently conclusive evidence that in this condition the symptoms arise as a result of a central stimulation which is emotional in origin. He has found that after mental or emotional rehabilitation, patients could perform exercise tests with normal cardiac and respiratory responses, whereas formerly these same exercises had caused marked disturbances in breathing. Moreover, in many patients there were spontaneous, sudden, inexplicable attacks of tachypnea or dyspnea occurring while at rest, accompanied by other evidences of sympathetic stimulation, indicating conclusively that these respiratory difficulties were of psychogenic or neurogenic origin.

It is difficult to believe that all these workers, using different groups of patients, in different countries, during war and peace, employing different techniques, could all make the identical mistake. On the contrary, the unanimity of opinion among recent workers is one of the strongest evidences that after three-quarters of a century, we can, at last state with confidence that all the various names proposed for DaCosta's syndrome should be discarded, and the proper psychiatric diagnosis used in each case, despite the strong objections of the average patient to being labelled as a psychoneurotic. Proper treatment and eventual cure of the condition will never be achieved so long as we continue to regard it as merely an abnormal response to effort or a functional abnormality of the heart or vasmotor system. It is my hope that many of you will be so dissatisfied with this very inadequate summary of the recent evidence that you will read at least several of the papers to which I have referred so briefly.

Rubella in Pregnancy: For an important contribution to our knowledge of etiologic factors in heart disease we are indebted to Australian physicians, especially to Gregg⁶ and Swan.⁷ Several years ago Gregg made the startling observation that congenital cataracts in infants were associated in a high percentage of cases with the occurrence of German

measles in the mother during the early months of pregnancy. Further studies in Australia, New Zealand, England, and this country⁸ have not only confirmed his original observations, but have also disclosed that rubella during the first few months of pregnancy is very likely to cause congenital anomalies of the heart, deafmutism, and other congenital abnormalities. Last year Swan and Tostevin⁹ reported a group of 56 mothers who had some form of infectious disease during pregnancy; 40 of these had rubella, the other 16 had measles, chicken-pox, mumps, herpes zoster, or scarlet fever. Of the 40 cases associated with rubella, 36 infants had congenital abnormalities, and 19 of these had evidence of heart disease. The authors emphasize that in a number of cases the heart presented no definite signs of disease on physical examination, but the organ was enlarged as shown by a standard six-foot film; they regarded the diagnosis as doubtful in 5 of the 19. In 15 of the 19 cases diagnosed as heart disease, the rubella occurred during the first 3 months of pregnancy; in the other 4 at 3½, 4, 4½ and 7 months.

A review of the literature pertaining to this dramatic discovery was published last year by Aycock and Ingalls.¹⁰ This indicated beyond reasonable doubt that rubella during the early months of pregnancy is associated in many cases with abnormalities in the infant. One cannot say that rubella always causes such abnormalities, or that it is the sole cause of them, but it is now possible to state with confidence that a baby is very likely to be deformed at birth if the mother acquires this disease early in her pregnancy. One hundred cases of such congenital abnormalities reported by eight different authors were analyzed by Aycock and Ingalls, who found that the rubella occurred during the first month in 30 cases, in the second month in 42, in the third month in 22, in the fourth month in 5, and in the sixth month in 1.

It is unnecessary to stress the great value of this knowledge, but perhaps it is well to remind you of the further implications of the discovery. It is immediately apparent that other virus diseases may also have a similar effect; indeed, in the report of Swan and Tostevin there were nine abnormal babies born of the sixteen mothers who had measles, mumps, herpes zoster, or chicken-pox during pregnancy. Studies upon this point are now going forward, which may lead to clearer understanding of this serious problem, and possibly to prevention of a large proportion of congenital malformations.

It is also clear that important sociological problems have been created by this recent knowledge, for the question of therapeutic abortion inevitably arises. The review by Aycock and Ingalls concludes with these words:

"Many authors have gone as far as to suggest that the justification for therapeutic abortion, if rubella (or other exanthemata) be contracted in the first two months of pregnancy, should be debated. Others have gone as far as to accept the available evidence as sufficient grounds for termination of the pregnancy. Such a far-reaching question can be approached with wisdom only when there are adequate statistical studies to establish the specific risks of infection at all stages of pregnancy. Knowledge from such studies would have to be interpreted not only in terms of actual risk of congenital anomalies, but as well in terms of the 'health of the mother' in continuing a pregnancy with such a known risk, and finally in terms of an informed public opinion."

Sodium: The introduction of radio-active isotopes, while still very recent, may result in significant advances in diagnostic and therapeutic methods in the near future. Most of you know that radio-active potassium has been used for several years in the treatment of polycythemia vera and skin cancer, and that radio-active iodine is now being employed in the treatment of diseases of the thyroid gland. An example of the possible diagnostic use of such isotopes has been provided by Dr. George Burch and his associates, whose beautiful exhibit dealing with the fate of sodium in the body must have been seen by many of you at the last Annual Session of the American Medical Association. Dr. Burch has graciously sent me the manuscripts of two unpublished papers which summarize much of the material displayed in that exhibit. It is these papers which form the basis for the following brief remarks.

Observations were made upon the relationship between weight, venous pressure, and the excretion of sodium in a normal subject, a patient recovering from congestive heart failure, and one whose heart failure was steadily increasing in spite of treatment.¹¹ The sodium excretion was followed by using radio-active sodium 22, which has a relatively long half-life of three years. It was found in general that the patients with congestive heart failure excreted less than normal amounts of sodium and water during the periods when heart failure was stationary or advancing, but greater amounts than normal during periods of improvement. The changes in weight and in venous pressure

were concordant—that is, they rose or fell practically simultaneously—but varied inversely with the excretion of sodium and water. However, a change in venous pressure or weight or sodium excretion could not be shown to precede a change in either of the other two. The normal subject had excreted 69 per cent of the injected sodium in sixty days, the patient who was improving had excreted 64 per cent, while the patient with advancing heart failure had excreted only 42 per cent at the end of two months. The findings were in accord with the generally accepted ideas of congestive heart failure, that is, if failure is present or increasing, the weight and venous pressure increase and there is an abnormal retention of sodium and water; during recovery the reverse is true. But Burch and his coworkers are careful to emphasize that the mechanisms concerned with retention of sodium and water in this condition remain unknown.

In a related study, Burch and his collaborators¹² used Na 24, which has a half-life of only 14.8 hours, to study the rate of diffusion of sodium through the vascular wall and its rate of excretion into the urine and sweat. Normal subjects and patients with congestive heart failure were used, and the sodium was administered by a single intravenous injection. It was found that sodium diffuses through the vascular wall at two rates, rapid and slow. In a normal subject the average rate of diffusion indicated that about 32 per cent of the total plasma sodium diffused out of the blood every minute. This approaches a diffusion across the vascular wall equal to about 18 pounds of sodium or 50 pounds of sodium chloride per day. The patients with congestive heart failure showed a more rapid rate of sodium diffusion from the vascular bed than did the normal subjects. These rapid rates of diffusion between the blood and the interstitial fluid, and the huge quantities of sodium involved, make it necessary to reconsider the role of sodium in edema formation. It is clear that relatively slight changes in the rate of sodium diffusion from the blood, and a disturbance in its excretion through the kidneys, might result in rapid and marked edema formation.

These papers from the New Orleans group are in the nature of preliminary reports but are of such fundamental importance that they must be extended. It seems probable that this new method may hasten our final complete understanding of the complex and very serious problem presented by fluid retention in congestive heart failure.

Surgery of Congenital Anomalies: It may seem to many of you a

waste of time to refer to the surgical treatment of congenital anomalies of the heart and great vessels, but no survey of the past few years can possibly omit this dramatic contribution. Indeed, it is so dramatic and has been so widely publicized in both the medical and lay press that there are probably few physicians who are not familiar with the broad features of the three operative procedures associated respectively with the names of Gross of Boston, Crafoord of Stockholm, and Blalock and Taussig of Baltimore. It has been only a short time since Gross first successfully ligated a patent ductus arteriosus, but there have been hundreds of patients subjected to this operation since he first demonstrated that it could be performed. As of October 1, 1941, he has himself performed either ligation or resection of the duct in 225 cases. In a letter to me of that date he says: "To date, I have operated upon 225 ductus cases. Forty-three were operated upon by some form of ligation—a procedure which I have now completely abandoned. In the last 182 patients the complete division of the ductus has been performed. I have never lost a patient during or after operation from the division technique itself. In the 182 cases with division there have been four deaths from various causes (one from staphylococcus mediastinitis, one from faulty anesthesia, two from cardiac failure). This gives a mortality rate of 2.2 per cent. This series obviously includes many patients who were excellent risks; it also includes a considerable number of patients who were exceedingly poor subjects for surgery. I feel that the operative risk in our experience for children is almost zero."

Most authorities are now agreed that such operation should be performed in almost every instance if the diagnosis is certain, since it apparently prevents the chief complications often associated with this condition, namely, stunting of growth, enlargement of the heart leading to congestive heart failure, and subacute bacterial endarteritis.

Secondly, it has been shown in the past several years that it is possible to eliminate the constricted portion of the aorta in patients who have the adult type of coarctation. In October 1944, Crafoord performed this operation successfully on two patients. Before these cases were reported in 1945 by Crafoord and Nylin,¹³ Gross had already performed successful extirpation of experimentally constricted aortae in dogs, and shortly after Crafoord's brilliant demonstration, Gross also operated successfully in human beings. On September 30, 1947 he wrote me as follows:

"In the coarctation work, I have operated upon thirty patients. I have backed out of four of these because it seemed that the anomaly was such that it could not be corrected by surgical means. In the twenty-six patients from whom the coarctation was removed there were four deaths from various causes. In the surviving twenty-two patients I have had one who had no relief from hypertension but in the remaining twenty-one subjects there has been an excellent reduction of the arterial pressure in the upper part of the body. In general, these operations have been quite satisfactory in young subjects—from seven or eight years up to about eighteen years of age. However, they are exceedingly difficult beyond this age, and there are disheartening returns, as far as satisfactory results are concerned, in older subjects (due largely to the sclerosis which occurs so early in the aorta of these patients)."

In point of time, the latest of the three dramatic surgical procedures applied to congenital malformations was that devised by Drs. Taussig and Blalock for the purpose of correcting at least some of the more serious features associated with the tetralogy of Fallot. The one important principle underlying this procedure is to supply additional blood to the lungs by suturing a normal artery (usually the subclavian) to one of the pulmonary arteries. In the great majority of cases this results in remarkable improvement in the condition of the patient.

It would be impossible to overestimate the value of these new procedures in improving or entirely curing several serious conditions of the heart and great vessels. I wish to join all other physicians in voicing gratitude for these new advances in a field where for generations treatment was regarded as impossible. It is not with any desire to minimize these great achievements that I feel it necessary to remind you that the total number of patients with these three conditions is very small in comparison with the number of those who have the acquired forms of heart disease. We cannot rest upon these laurels, but must still seek measures that will diminish or abolish hypertension, rheumatic fever, and coronary atherosclerosis.

Low Sodium Diet and Unrestricted Fluids in Congestive Heart Failure: In my judgment, one of the very important advances of recent years in the realm of therapy is the steadily widening recognition of the importance of low sodium, high fluids, and an acid reaction of the diet in the treatment of congestive heart failure with edema. In 1941

Schroeder¹⁴ showed that the restriction of salt to an amount below that excreted in the urine always resulted in a decrease of edema. When salt was restricted to amounts less than 1.0 Gm. per day, restriction of fluids was unnecessary; indeed, he noted that diuresis sometimes occurred when the patient was taking fluids liberally, and that it might cease when fluids were restricted. He concluded that restriction of salt was important in treating the edema of congestive heart failure, but that restriction of fluids was of little value.

Long before Schroeder reported this significant study, Schemm had been following a plan of treatment which recognized the importance of restricting sodium, but went much farther. The fundamental principles underlying this will not be discussed in detail, as they are clearly and logically presented in Schemm's three important papers.¹⁵ Briefly, as enunciated by him, these are: 1) Each liter of edema fluid contains about 10 grams of an alkaline mixture of sodium salts and 1000 cc. of water. This edema fluid is subject to the same vicissitudes as the normal interstitial fluid; some of the water may be given up for vaporization, and the edema fluid consequently become more concentrated; in these circumstances, the patient may be severely dehydrated, even in the presence of massive edema. 2) The alkaline edema fluid remains in the tissues indefinitely unless the bicarbonate fraction of its sodium salts is used up by the constantly forming metabolic acids or by ingested acids. Acidification incites the kidneys to eliminate neutral or acid sodium salts; the water in which they were dissolved may be eliminated through the kidneys (diuresis) or may remain within the body to correct body fluid concentration and cellular dehydration, thus causing a disappearance of edema without weight loss and without diuresis. 3) Water reaches the kidneys for the formation of urine only after all the other needs of the body for water have been met; therefore, enough water must be administered by mouth or parenterally to meet these other bodily needs and supply an excess for the excretion of sodium. In most cases this means quantities of 3 to 6 liters of water per day. On the basis of these concepts, Schemm recommended a regime which would: 1) decrease the ingestion of the material essential for the formation of edema, and encourage the mobilization of the sodium already retained, by providing a diet very low in sodium and yielding a neutral or acid ash; 2) increase the normal effect of the metabolic acids by the administration of small amounts of acid drugs; and 3) facilitate the elimination

of the mobilized sodium through the kidneys and avoid the development of cellular dehydration by administering plain water in amounts that are adequate according to the established principles of water-balance.

It is perhaps not surprising that doctors in general have been slow in accepting this important contribution nor that today one frequently encounters physicians who have not taken the trouble to ascertain why it is logical to force fluids in the presence of edema. If they have the courage to try this form of treatment in spite of misgivings, they usually stop it abruptly if the patient gains weight or has a slight increase in symptoms during the first one or two days. But this is not a new and untried method; Schemm's first report in 1942 was based on the analysis of approximately 600 periods of treatment in 400 patients, of whom 375 had serious heart disease and more than 200 had gross edema. So far as one may judge by published reports, this treatment was largely ignored for several years, but recently has been attracting wide and favorable attention. Of the reports now available, brief mention will be made of only two. Leevy and his co-workers¹⁶ used the low sodium diet in a group of 122 patients with congestive heart failure. In some the fluids were restricted, in others fluids were allowed as freely as desired, and in still others the total intake of liquids was forced up to 3000 cc. per day. They state: "With restricted sodium intake, restriction of water is unnecessary in treating cardiac decompensation, increases the discomfort of the patient and may prove deleterious". They found that forcing fluids had little effect upon the rate of improvement of most patients with congestive heart failure.

Wheeler, Bridges, and White¹⁷ have recently reported the results of this regime in a group of 35 patients with congestive failure. They state that the results were excellent in 22, and that no patient was made worse by the administration of fluids in large quantities. It should be noted that the total amount of fluids administered to the patients in these two studies was considerably less than those advocated by Schemm, and it is not clear that attempts were made to provide an acid ash diet, but rather one with a neutral ash. To this extent they cannot be regarded as tests of the strict Schemm regime. I can testify from personal experience that strict adherence to Schemm's plan sometimes leads to highly satisfactory results when even slight modifications have been less successful.

There are few experiences so gratifying as to place a chronically waterlogged patient on this treatment and watch the steady improvement that follows, with the accompanying rise in the morale and courage of the patient. It would be difficult for me to express adequately my admiration for this splendid contribution, and the least I can do is to urge all of you who are not familiar with it, and who may be responsible for cardiac patients, to read Schemm's papers and give his plan the benefit of careful trial.

Coronary Atherosclerosis and Cholesterol: One of the most serious problems relating to heart disease in the adult is the appalling incidence of coronary arterial disease. It is surely unnecessary to remind you that each year thousands of apparently healthy men between the ages of 20 and 50 years are killed or reduced to invalidism by sudden and unexpected manifestations of coronary insufficiency or coronary thrombosis. For many years students have been trying to learn why changes occur in the intima of human coronary arteries that lead to gradual or sudden occlusion, why such changes affect the male so much more frequently than the female, whether there is any way of preventing or retarding these pathologic processes, and what part is played by cholesterol. It is perhaps impossible to give final answers to these questions, but progress has been made in the past few years, and some of this may be indicated briefly.

With regard to the much higher incidence in the male sex, Dock¹⁸ has recently made observations of great significance. In studying the epicardial coronary arteries of newborn infants, he found that the intima was much thicker in males than in females, and he believes this establishes the basis for the sex difference in the incidence of coronary thrombosis. Careful measurements of the intima and the media of these arteries showed that the average intima in newborn males was 26.5 per cent the thickness of the media, while in females it was only 8.2 per cent. In Dock's words: "The male therefore begins life with about three times as much coronary intima as the female." This very important observation should be confirmed in a much larger series of infants, but there is no reason to question its essential accuracy. Dock is careful to point out that it throws light chiefly upon the sex incidence of coronary arterial disease, and states that hypertension and faulty cholesterol metabolism are the most important immediate causes.

Hypertension will be considered later; for the moment let us review

in a most inadequate way some of the present knowledge relating to cholesterol. There are many facts that point to a close relationship between this substance and coronary atherosclerosis. It is known, for example, that cholesterol in the blood serum rises to high values in those diseases which are associated with advanced coronary atherosclerosis, even in young patients; these diseases include uncontrolled diabetes, myxedema, familial xanthomatosis, chronic glomerulonephritis in young people, and some cases of obesity. It is known that cholesterol is deposited in the walls of coronary arteries, and it appears to be directly responsible for thrombosis in a large number of cases. Steiner and Domanski¹⁹ have shown conclusively that the average level of the serum cholesterol is much higher in patients with coronary disease than in control subjects, and that it also fluctuates more widely. Coronary disease is said to be relatively rare in those races, such as the Chinese, who live on a diet low in cholesterol. Arterial lesions are readily induced in rabbits by the feeding of this substance, but this observation has been regarded as rather inconclusive because of the herbivorous nature of the experimental animal and the frequency with which it develops arterial disease spontaneously or in response to various factors. However, Steiner and Kendall²⁰ have recently succeeded in producing arterial lesions in dogs similar in distribution and morphologic character to those seen in human atherosclerosis and arteriosclerosis by inducing prolonged hypercholesterolemia and simultaneously depressing thyroid function by means of thiouracil. It had been shown previously that prolonged elevation of the serum cholesterol alone did not produce such lesions.

It is widely believed, and frequently stated, that the amount of cholesterol in the serum of humans cannot be influenced by diet,²¹ but there is apparently insufficient evidence to support this categorical statement. It is true that the level remains fairly constant in normal people, and it seems clear that it is not altered appreciably by a single large feeding of cholesterol, or even by feeding large quantities for several days. It is known that the body can synthesize this substance from foods other than those containing cholesterol. But it has been shown conclusively that the serum level can be raised by 30 to 50 per cent or more in monkeys,²² dogs, and humans by feeding egg-yolks for days or weeks, and that the level falls to normal after such feeding has been discontinued. Steiner and Domanski²³ found that the administration of 100 Gm. of egg yolk powder per day for six to ten weeks caused an increase of

the serum cholesterol from 50 to 218 mgm. per cent, the average rise being 101 mg. per cent. Okey and Stewart²⁴ showed that there was a slight consistent rise in the serum cholesterol in a group of normal women fed four egg yolks daily. Kempner²⁵ has reported, in a lecture given at this Academy, that the average fall in cholesterol of 79 patients on a rice diet was from 243 to 189 mgm. per cent. Dr. Steiner²⁶ tells me that some of his patients show at least a moderate reduction in the serum concentration when placed on diets low in fats and cholesterol, and I am able to confirm this statement on the basis of personal observations upon a small group of patients. Adlersberg,²⁷ Steiner and Doman-ski,²⁸ and others have shown also that the level can be appreciably lowered by the administration of soya lecithin but this effect continues for only about five weeks, after which it gradually ceases, even though lecithin is continued. A consideration of this and other evidence leads me to the conclusion that the serum cholesterol in humans is not entirely independent of diet.

The observations just enumerated seem to me of probable great significance, but they cannot be regarded as wholly conclusive. There are still many and wide gaps in our knowledge of the absorption, utilization, synthesis, and deposition of cholesterol in various tissues. It seems probable that a fundamental fault in the metabolism of this substance is responsible for the high serum levels that are found in certain diseases, and there are some thoughtful students who seriously question whether a high concentration of cholesterol in the blood does *of itself* lead to coronary atherosclerosis. So far as I am aware, there is no direct proof that lowering of the serum level by means of diet or lecithin prevents further changes in the coronary arteries of those who have already suffered thrombotic closure of these vessels. Obviously it will be difficult to secure such proof. The evidence available today is indirect but strong, and to me it appears to justify the tentative conclusion that a high level of cholesterol in the blood serum is probably dangerous, and that efforts should be made to reduce it to normal.*

A moment ago I alluded to the recent report of Steiner and Kendall,²⁹ indicating that arterial lesions similar to those of humans have

* While the present paper was in press, further significant observations upon the probable relationship between high serum cholesterol and coronary atherosclerosis have been published by Boas, Parets, and Adlersberg (Hereditary disturbance of cholesterol metabolism: a factor in the genesis of atherosclerosis, *Am. Heart J.*, 1948, 35: 611).

been produced for the first time in dogs by the maintenance of hypercholesterolemia for some months. If they or others prove that such lesions can be produced uniformly in such animals by this means, it will provide powerful, but not absolutely conclusive, evidence that an excessive amount of cholesterol in the serum is one of the important factors in the etiology of intimal changes in the coronary arteries. It will also provide us for the first time with an experimental method for the careful and controlled study of the development of these changes, and this may well lead to the discovery of means for retarding or preventing them.

Anticoagulants in the Treatment of Cardiac Infarction: Several years ago Nichol and Page²⁹ reported their observations upon the use of dicoumarol in patients who had sustained coronary thrombosis. The purpose of administering this anticoagulant was to prevent extension of the original thrombus as well as the formation of new thrombi in the heart or in the systemic veins. Their experience seemed encouraging. Within a very short time similar reports, with equally gratifying results, appeared by Peters et al³⁰ and by Wright.³¹ Dr. Wright was so impressed by the possible importance of the treatment, and by the necessity of determining its value at the earliest possible time, that he proposed a coöperative study, to be undertaken under the auspices of the American Heart Association and carried out in fifteen or more hospitals throughout the United States. It was his belief that it would be necessary to have careful and conclusive studies upon not less than a thousand, and preferably several thousand, cases and an equal number of controls. It is encouraging to be able to report that his suggestion was received with enthusiasm by the directors of the American Heart Association, and that financial support of the project was received from the U. S. Public Health Service. Under a committee representing every participating hospital, and under the able chairmanship of Dr. Irving Wright, the study has now been under way for almost a year. Under the plan adopted, all patients with acute coronary thrombosis who are admitted on odd days of the month are treated with dicoumarol; all who enter on even days of the month are kept as controls. Actual figures cannot be given today, but a preliminary analysis of the results in June 1947 showed a remarkable difference between the two groups. If such a difference is maintained throughout the study of one or two thousand cases, it seems certain that the use of dicoumarol will

be a magnificent contribution to the treatment of this serious condition.*

Penicillin for Treatment and Prevention of Subacute Bacterial Endocarditis: It is probable that very few discussions of treatment could be complete if they did not include penicillin, and the present one is no exception. Until very recent years the treatment of subacute bacterial endocarditis was generally regarded as practically hopeless, despite an occasional success from the use of one of the sulfa drugs. Loewe deserves great credit for having demonstrated the value of large doses of penicillin in this disease after the Penicillin Committee had officially declared it to be of no value. Following his reports of cures after using quantities of penicillin far larger than had previously been tried, success was achieved almost uniformly, and today it is possible to state that the great majority of patients with this infection can be cured if sufficient amounts of penicillin are administered.

But there is another use of this miraculous substance that may prove to be even more important. It has been shown³² that transient bacteremia follows tooth extraction in as many as 70 per cent of cases, and the *Streptococcus viridans* is the invading organism in almost all of these. Last year Favour, Janeway, and Levine³³ reported a series of 21 patients with bacterial endocarditis, in 10 of whom there had been tooth extraction, dental procedures, or obvious tooth infection preceding the onset of the endocarditis. The probability of a causal relationship between dental procedures and subsequent infection of the heart is of such great importance that further study is urgently necessary; at the moment, it seems altogether probable that extraction of teeth and other forms of oral surgery are hazardous procedures in any patient who has rheumatic heart disease or a congenital anomaly. The American Council on Rheumatic Fever of the American Heart Association has officially recommended that all such patients receive penicillin in adequate dosage just before and for some days after extraction of teeth or any other surgical procedure within the oral cavity. It is hoped that this prophylactic measure will soon become routine and compulsory throughout the civilized world.

Prevention of Recurrent Rheumatic Fever: Brief mention should be made of a similar preventive method that is being widely applied

* Some months after the present talk was given, analysis of 1000 treated and 1000 untreated cases revealed that the mortality rate among those receiving dicoumarol was 13%, while in the untreated group it was 23%. The incidence of thrombo-embolic complications was 19% in the untreated cases but only 9% in those treated with dicoumarol. The actual number of such complications was 36 per 100 patients in the control group, and 8 per 100 in the treated group.

to rheumatic fever. It is probable that no one can speak with absolute certainty on this point, but there is a good deal of evidence in support of the belief that the routine daily administration of sulfa drugs in small doses to children who have had one attack of rheumatic fever may prevent subsequent attacks. The work of Kuttner and Reyersbach³⁴ at Irvington House showed conclusively that in a closed institutional population this was true. It is too soon to state positively that the drug will be equally effective in large groups of children scattered through the homes of a large city and exposed to conditions that did not exist at Irvington House. But the experience thus far seems to have been favorable, and it is quite possible that in a few years we may find a great reduction in the incidence of rheumatic heart disease because of the prevention of rheumatic recurrences by this drug.

Hypertension: We come finally to a consideration of another of the serious and baffling medical problems—hypertension. Undoubtedly many of you will consider me as incorrigibly optimistic in thinking that there has been any progress in the treatment or prevention of this condition, and you may be right in that conclusion. But there are several aspects to which your attention is invited for a moment.

The forms of treatment advocated in recent years in addition to general medical oversight and symptomatic therapy have been chiefly three in number—dorso-lumbar sympathectomy of varying extent, exemplified well by the Smithwick technique, the rice diet of Kempner, and a diet low in sodium but not restricted to rice. I shall say but little with regard to the results of sympathectomy, for two reasons. One is that Smithwick's cases have been analyzed with great care, unusual insight, and exceptional clinical judgment by Palmer³⁵ whose paper is commended to all of you interested in this subject. The other is that one week from today in this Academy, Dr. Hinton of this city is to analyze the results in 440 hypertensive patients subjected to this procedure. It was my privilege to hear him present the analysis as of April, 1947 before the Connecticut State Medical Society, and brief reference may be made to one feature of his work that has already been published.³⁶ He and his associates have now adopted a system of rules which leads to a higher rejection of cases and an operative mortality of zero up to the time of his report. These rules are based upon a classification of the degree of change in four organs, namely, the eyes, brain, heart, and kidneys. Such changes are graded from 0 to

plus 4, and the sum of all plus signs determines whether or not operation should be performed. But Hinton states frankly that no entirely satisfactory method has yet been found for the selection of patients for sympathectomy; after all objective studies have been made, the decision must still rest to some extent on clinical judgment. His analysis of a large but selected series of his patients indicates a high percentage of improvement, both subjective and objective, after periods varying from 6 to 36 months.

No personal analysis of the results obtained by Smithwick will be attempted, since this has already been done by Palmer, from whose paper several excerpts will be read:

"A major effect of dorsolumbar sympathectomy in essential hypertension results from the relative postural hypotension, pooling of the blood in dependent parts and presumed decrease in venous return. The duration of this effect varies widely, lasting from months to years, and accounts for much, if not the major part, of both the favorable effect on the disease and the considerable disability associated with the operation.

"When the favorable effect of operative intervention is critically evaluated (persistent reduction of the blood pressure to 150 systolic and 110 diastolic or below in all positions), it is found that in the present series there has been a diminishing return of favorable results the longer the patients are followed; nearly 70 per cent early in this experience, declining to 25 per cent when patients are followed three to five years or more. But this effect has been obtained twice as frequently in this series by surgical means as by a careful medical regimen and was obtained in patients with malignant hypertension whose blood pressures were unaffected by medical management.

"From this experience sympathectomy is regarded as the treatment of choice, at this time, for malignant hypertension and may be offered to patients with early or moderate vasospastic hypertension who have no clinical evidence of advanced, irreversible, diffuse arteriolar disease.

"Prescription of operation for the patient with hypertension involves evaluation of the hypertension and attendant organic changes, the social and economic status and the personality of the patient and the objective of treatment (symptomatic relief, reduction of the blood pressure or halting the progress of the disease). Final judgment may depend on balancing the present status and estimated future of the patient with induced discomfort and disability."

No reference to this subject would be complete if it did not include mention of the work and opinion of Dr. William Goldring. He advances powerful arguments against the belief that sympathectomy is an important method of treatment, although admitting that it is the best for the alleviation of certain symptoms, especially headache. His paper which appeared February 1947³⁷ is a scholarly, thoughtful, and very fine discussion of both the medical and surgical management of hypertension.

Of the two other methods that are now being tried, the better

known is the rice diet of Kempner, which consists of rice cooked without salt, sugar, fruits, and fruit juices. No salt is permitted. Kempner³⁸ states that the average patient can eat 6½ to 10 ounces of rice per day, which provides 700 to 1000 calories; the remainder of the caloric requirements must be met by the use of sugar and fruits. Despite the low protein intake, the protein equilibrium of the patients is maintained, while the chlorides in both urine and plasma decline sharply.

Of the patients in whom the non-protein-nitrogen was determined, it remained stationary or increased in 24 per cent, and declined in the other 76 per cent from an average of 53 mgm. per cent before the diet to 36 mgm. per cent after an average of 78 days on the diet. The serum cholesterol declined in 73 of 82 patients from an average of 266 mgm. per cent to an average of 183 mgm. per cent after 91 days on the diet. Of 53 whose cholesterol was 220 mgm. per cent or more, it fell in 52, and in 37 of these it reached normal levels.

Kempner's first extensive analysis considered 192 patients with hypertension on the basis of acute or chronic primary kidney disease or with "hypertensive vascular disease." Of these, 25 died after following the diet for 6 to 81 days, the average being 25 days. Of the remaining 167 patients Kempner states that there was improvement in 64 per cent and no improvement in 36 per cent. It should be noted, however, that in this analysis he does not include the 25 patients who died after an average of 25 days on the diet. Presumably these are to be regarded as failures; if they are so regarded and are included in the analysis, we find that there was improvement in 56 per cent and no improvement in 44 per cent. Stated otherwise, slightly more than half of the patients improved, and slightly less than half failed to improve.

There were 31 patients whose electrocardiograms showed inversion of T 1, and in 11 of these the T waves became upright after varying periods on the rice diet.²⁵ The size of the heart as measured in x-ray films decreased in 77 of 87 patients. Retinopathy decreased greatly or cleared up completely in a number of those whose blood pressure was reduced.

It would be foolish to state that the strict rice diet is valueless in the treatment of hypertension, for many patients have been demonstrably and greatly improved. But it would be equally foolish to assume that all patients will tolerate the diet, for many have refused to continue it after longer or shorter periods, stating quite frankly that they

would rather die of the disease than suffer the torments of eating rice three times a day for interminable weeks or months. Any estimate of the value of the treatment must consider at least two questions: 1. How well and how long does the average moderately sick person adhere to the strict rice diet? 2. Is the rice itself the important therapeutic agent, or is the improvement due largely or entirely to the absence of sodium? An accurate answer to the first question is not yet available, but it is certain that some patients who have taken the rice diet faithfully for months finally declare that further continuation is impossible. Whether this number is large or small is still undetermined; on the basis of my own limited experience it seems probable that a fairly large percentage lack the grim determination that is necessary to adhere to a diet that is extremely unpalatable and psychologically depressing. With respect to the second question information is beginning to accumulate; Dr. George Perera has recently reported³⁹ that hypertensive patients whose blood pressure had been moderately reduced by a strict rice diet could be changed to a general mixed diet very low in sodium without any rise in the blood pressure. If the rice diet was resumed, the pressure remained unchanged. In other words, the blood pressure remained at the same level if the patients used a strict rice diet or a general diet very low in sodium. Several of my patients who had been on the strict rice diet for many months have now been using a liberal diet low in sodium for periods of six to nine months. In none has there been a rise in the blood pressure or any evidence of diminution in renal function. The patients have gained in weight and strength and are far more cheerful; while on the rice diet they were extremely depressed.

It is my own present impression—and I state it only as an impression—that it is the very low sodium content of the rice diet which accounts for its effectiveness in the 50 to 60 per cent of hypertensive patients who show improvement. This impression is strengthened by the experiences of Grollman et al,⁴⁰ whose report upon five patients appeared two years ago. They used diets containing 2000 calories and less than 1 Gm. of sodium chloride. In two of the five patients the blood pressure declined to normal levels, rose again when NaCl was added to the diet, and once more fell to normal when salt was withdrawn. A third patient displayed moderate reduction of the pressure. A fourth had no reduction of pressure within several weeks. The fifth

had carcinoma of the liver in addition to hypertension; the reduction of sodium had no effect upon the blood pressure in this patient until a collapse reaction developed. There was prompt recovery following the administration of saline solution. This was the only one in whom the restriction of sodium caused any harmful effects. These observers employed low sodium diets because they had previously found such diets effective in reducing the elevated blood pressure of rats with experimental renal hypertension.

Let me conclude the inadequate discussion of this topic by expressing the personal view that we cannot as yet make any final appraisal of the three methods just mentioned. That each one has been effective in reducing blood pressure and abolishing symptoms for short or long periods in a certain percentage of patients cannot be questioned by any fair-minded person; that each one has serious shortcomings as a method of treatment must also be admitted. It is my belief and very earnest hope that all three will be abandoned within a short time, but until the specific cause or causes of human hypertension have been discovered and specific remedies found, it is of the utmost importance that low sodium diets should be given extensive and critical trials. In my opinion sympathectomy is a justifiable procedure in carefully selected patients with malignant hypertension and in a few of those whose pressures and symptoms are disabling and have not responded to any other form of therapy.

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JAMES ALEXANDER MILLER

1874-1948

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Dr. James Alexander Miller, thirty-sixth President of The New York Academy of Medicine died on the 29th day of July 1948 in his seventy-fifth year. Thus ended one of the most distinguished careers in the history of American Medicine.

Born March 27, 1874, he graduated from Pingry School, Elizabeth, New Jersey, at the age of fifteen, and entered Princeton in the fall of 1889. Always a student, he maintained a high scholastic standing, especially in Chemistry and Latin, and yet he was in no sense a "grind." He found time to play and attained as high a degree of efficiency in the games he chose to play as he did in scholarship.

He received his A. B. in 1893 and A. M. in Chemistry in 1894, and at the age of twenty entered the employ of the New Jersey Zinc and Iron Company in Elizabeth, New Jersey as chemist. After a few months with this company Dr. William H. Park, Director of Research Laboratories of the New York City Department of Health offered him the position of Research Chemist which he accepted.

Dr. Hermann M. Biggs, who had watched his work, urged him to study medicine, and in the fall of 1895 he entered the College of Physicians and Surgeons, retaining his position in the Laboratory during his first year. In the Medical School he partly supported himself by tutoring. Graduating among the first ten men in his class, he thereby qualified to compete for the Harsen Prizes for proficiency in examinations, and won the first prize of \$500. He also won first place in competitive examination for internship at Presbyterian Hospital out of a field of twenty-nine candidates.

Immediately after completing his internship, he began the practice of medicine in the summer of 1901 at Paul Smith's in the Adirondacks, and continued his practice there for eight summers. There began his long and intimate friendship with Dr. Edward Livingston Trudeau, who was largely responsible for directing his interest to the

field of pulmonary diseases, especially tuberculosis. Dr. Trudeau, when asked once about Dr. Miller, replied in his droll way: "Miller?—why he is all right. He can hear everything in a chest that I can."

In the fall of 1901 he started practice in New York City, and became associated with Dr. A. A. Smith. That association continued for over ten years.

In 1903 he began his connection with Bellevue Hospital as Adjunct Assistant Visiting Physician. That connection was unbroken until his death. He was Secretary of the Medical Board from 1918 through 1927. He conceived, organized and developed the Bellevue Hospital Chest Service, the most outstanding service of its kind in the city and probably in the country. It will be a lasting memorial to him.

In World War I, at great personal sacrifice, he served in France with the American Red Cross with the rank of Major, from June 1917 to November 1918, ten months of which time he was assigned to work with Dr. Livingston Farrand as Associate Medical Director of the Rockefeller Commission for the Control of Tuberculosis in France. France honored him by making him a Chevalier of the Legion of Honor.

Dr. Miller was connected with many hospitals during his life, as Attending or Consulting Physician. He was still on call to the Post-Graduate, Woman's, Methodist of Brooklyn and the House of Rest, Sprain Ridge, Yonkers. He was also Consulting Physician to the Trudeau Sanatorium, of whose Board of Trustees he was President from 1927, declining re-election in 1945.

In spite of his multifarious and exacting professional duties he was interested in many other activities. He was a former President of the National Tuberculosis Association and the New York Tuberculosis and Health Association, in the formation of which he took a leading part. He was a member of the Board of Managers of the Community Service Society, a merger of

the Charity Organization Society and the Association for Improving the Condition of the Poor, on one or both of which organizations' governing boards he had served for over thirty years. He became an active member of the Milbank Memorial Fund in 1922, and served until January 1948. He was elected Alumni Trustee of Columbia in 1945.

Dr. Miller was a former President of the Practitioners Society, the American Climatological and Clinical Society, the American College of Physicians and the New York Medical and Surgical Society. He was also a member of the Association of American Physicians and the American Association of Thoracic Surgeons.

His term as President of the College of Physicians was a most important one. He insisted that the Annual Meeting in his presidential year should be held in New York City, the first time it had ever been held there. He worked tirelessly to make it what was generally admitted the best meeting the College had yet held. It was largely due to his enthusiasm that the College acquired its attractive and hospitable headquarters in Philadelphia. He was on the College's Board of Regents for many years, and in recognition of what he had done for it and the profession, he was made a "Master" in 1943.

His service to The New York Academy of Medicine, to which he was elected in 1904, really began in 1911 when he was appointed to the newly authorized Committee on Public Health, now Public Health Relations. He was elected its first Secretary and served as such till 1928, when he became Chairman. It is difficult to think of that Committee without associating it with Dr. Miller, for he worked tirelessly for it for over thirty seven years. He was elected President of the Academy for the years 1937 and 1938, and did much to stabilize its finances and to bring about better coöperation with associated societies. He served on the Board of Trustees from 1925 until 1943 when he declined renomination. He also served most helpfully during a number of years on the Committees on Budget, Gifts and Bequests, to Investigate Problems Related to Medical Practice, and

Medicine and the Changing Order.

Dr. Miller was one whose services and attainments were bound to be recognized during his life. He was awarded the Honorary Degree of Doctor of Science by Columbia in 1930; by Princeton in 1936; and Doctor of Public Health by New York University in 1937. In 1944 the National Tuberculosis Association voted him the Trudeau Medal "for meritorious contribution in the Cause, Prevention and Treatment of Tuberculosis." A little more than a year ago, at the Convocation closing the Centennial Celebration of the Academy, he, "the Academy's most distinguished and beloved Fellow, and one of the greatest benefactors of mankind," was awarded the highest honor the Academy can bestow: the "Academy Medal." In May 1947, fifty-eight years after he had graduated, the Alumni Association of the Pingry School voted him its "Award for Winning his Letter in Life."

Dr. Miller was an extraordinarily able man. Endowed with a fine mind, he developed it to the highest degree. He was wise in counsel; discerning in judgment; unfailing in leadership, with a limitless capacity for work. When he started anything, he never stopped until the job was completed. He gave of himself without stint. He had vision; was a straight thinker and was able to crystalize his thoughts. With it all he was intensely practical, and a wonderful judge of men. He knew how to arouse interest in a problem, and how to keep that interest. Even the politicians of the day listened to him and respected him.

He had a keen sense of kindly humor. He had a love of people and boundless kindness toward people. That is why his patients believed in him, trusted him implicitly, and never forgot him. One wrote to Mrs. Miller: "I have come to look upon him*** as a warm-spirited friend whose sympathy and understanding were a wonderful help in some dreadfully dark hours.*** Dr. Miller earned high honors during his long and busy career, and he deserved them richly; but I like to think that his greatest monument is in the hearts of all of us whom he led strongly by the hand on the long hard climb from the neighborhood of death back into the sunshine again."

His character was not one sided. While he had a great capacity for work, he also had a great capacity for play, and when he had the opportunity in his busy life, he played as he had worked, with great skill, enthusiasm and with his characteristic will to win.

"He lacked none of those attributes one would expect to find in the good Christian

man that he was. He was an elder of the Brick Presbyterian Church for many years."

Granted that in this world of ours no individual is indispensable, no loss irreparable, it is difficult to believe that any who knew Jim Miller will ever cease to miss him as adviser, leader, physician and FRIEND.

MALCOLM GOODRIDGE
PHILIP VAN INGEN

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
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DECEMBER 1948

SURGICAL TREATMENT OF GASTRIC,
DUODENAL AND GASTROJEJUNAL
ULCER, INCLUDING THE PRESENT
STATUS OF VAGOTOMY*

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THE concept is gradually being accepted that recurrent gastroduodenal ulceration is a psychomatic disease. It has for its basis certain types of emotional conflicts, aggravated by adverse environmental factors. It is influenced in part by dietary indiscretions and seasonal variations. The increased secretion of acid, a potent factor in the production of many ulcers, is probably the result of psychic disturbances, but it is not the sole cause of the ulceration, because there are innumerable individuals with a definite hyperacidity who never develop an ulcer. In its inception, peptic ulcer is a problem for the internist, the gastroenterologist and the psychotherapist. It only becomes a surgical problem when an acute perforation occurs, when the symptoms remain refractory to medical treatment, when hemorrhages recur, when a pyloric stenosis becomes intractable to therapy and when in the presence of a gastric ulcer a carcinoma is suspected.

* Address given as Friday Afternoon Lecture of The New York Academy of Medicine, March 5, 1948.
From the Surgical Service of The Mount Sinai Hospital, New York, N. Y.

The operative procedures which have been employed in the treatment of peptic ulcer have undergone an interesting evolution. At first these were directed primarily to the relief of mechanical obstruction of the pylorus, accomplished by pyloroplasty and gastroenterostomy. However, these simple drainage procedures often failed to give permanent relief, and it soon became apparent that gastroenterostomy, while it usually healed the duodenal ulcer, was complicated subsequently by gastrojejunal ulceration in 16 to 33 per cent of the cases. When the increased production of acid in patients with an ulcer diathesis was recognized as an important factor in the genesis of ulcer, and as the knowledge of the physiology of gastric secretion progressed, a more rational approach to the surgery of ulcer was developed. In brief, the three phases of gastric secretory activity have been recognized as 1) the cephalic or psychic phase, 2) the chemical phase, and 3) the intestinal phase. Inasmuch as the impulses controlling the psychic phase of gastric secretion are mediated through the vagi, it would seem logical to interrupt these nerves to the stomach in an effort to lower the gastric acidity. With this idea in view, many techniques were devised and described from 1920 to 1924 for the division of branches of the vagus nerves to the stomach below the diaphragm by Stierlin,¹ Bircher,² Latarjet³ and Schiassi⁴ respectively, and they reported good results in the treatment of peptic ulcer. With the possible exception of Latarjet, who advised an additional gastroenterostomy, all the aforementioned surgeons employed partial rather than total vagotomy. This may have been done for any one of several reasons. The belief that partial vagus section would accomplish the same objective; the opinion that total section would constitute too difficult a feat; and the fear of possible harmful physiologic effects upon other organs if complete vagus section were done. Evidently these procedures involving division of the vagus nerves were soon submerged by the rising tide of enthusiasm for subtotal gastrectomy for duodenal ulcer advocated by Von Haber, which occurred about this time. In this operation the pylorus and antrum are resected. With the eradication of these areas of hormonal production responsible for the chemical phase of gastric secretion, gastric acidity should be so reduced or further neutralized by duodenal regurgitation that it is no longer a major factor in the production or perpetuation of an ulcer. While subtotal gastrectomy of the Billroth II type has proven to be effective in the majority of cases of ulcer and has gained great popu-

larity in the past twenty-five years, it has not met with universal approbation. There have been objections to subtotal gastric resection on the grounds that in the hands of the average surgeon the operative mortality is significant, and that the magnitude of the procedure is not justified by a careful review of the follow-up results. After this operation many patients have failed to gain weight, and suffer from a serious train of symptoms known as the "dumping syndrome" and recurrent gastrojejunal ulceration, manifested by pain and hemorrhage, has been reported in from 3 to 9 per cent of the cases. It is unfortunately true that there are patients following adequate subtotal gastrectomy who develop recurrent gastrojejunal ulcerations, gastric and jejunal erosions, and in whom large quantities of hydrochloric acid are still secreted despite the elimination of the chemical phase of gastric secretion.

Klein⁵ in 1929 published the results of left vagus section combined with partial gastrectomy for duodenal ulcer when accompanied by a high preoperative acidity, and in 1938 Winkelstein and Berg⁶ reported their follow-up results with the combined procedures in thirty-four selected cases, in which twenty-six developed an achlorhydria, sixteen immediately and ten subsequently. Jejunal ulcers rarely develop in the presence of an anacidity and recurrent gastric ulcers have been known to disappear when an anacid medium was produced. Therefore it might be reasonable, in order to produce an achlorhydria, or markedly diminish the free hydrochloric acid, to eliminate the psychic phase of gastric secretion by complete vagus section in those cases in which a subtotal gastrectomy had already been done, in which a jejunal ulcer subsequently developed in the presence of free hydrochloric acid. Accordingly, in 1939, in an attempt to perform a complete division of the vagi, I performed a transthoracic bilateral vagotomy just above the diaphragm in two cases of gastrojejunal ulcer following subtotal gastrectomy. The first patient died on the fourteenth postoperative day, and post-mortem revealed a hemorrhage into a solitary adrenal gland. Two small chronic stomial ulcers were present, and while both main trunks of the right and left vagus nerves had been divided, there were still intact vagal fibers present, above and below the point of section. The second case,⁷ in which a previous prepyloric Ausschaltung had been done, developed a hemorrhage within one and one-half years. The insulin test in this case showed that the vagotomy had been incomplete.

Dissatisfied with subtotal gastrectomy as a procedure for duodenal

TABLE I—SUMMARY OF 126 VAGOTOMY CASES

<i>Surgical Approach</i>	<i>Procedure</i>	<i>No. of Cases</i>	<i>Diagnosis</i>
Supradiaphragmatic 33 Cases	Vagotomy alone	20	Duodenal ulcer
		1	Gastric ulcer
		2	Gastrojejunal ulcer post gastroenterostomy
		10	Gastrojejunal ulcer post subtotal gastrectomy
Infradiaphragmatic 93 Cases	Vagotomy alone	1	Duodenal ulcer
		5	Gastrojejunal ulcer post gastroenterostomy
		7	Gastrojejunal ulcer post subtotal gastrectomy
	Vagotomy plus gastroenterostomy	26	Duodenal ulcer
	Vagotomy plus subtotal gastrectomy	50	Duodenal ulcer
		1	Gastric ulcer
		3	Gastrojejunal ulcer post gastroenterostomy

ulcer, Dragstedt and Owens,⁸ turned their attention again to the effects of vagotomy in the therapy of peptic ulcer. In 1943 they reported their first two cases of supradiaphragmatic vagotomy as a sole procedure, advocating it in cases of chronic duodenal ulcer without stenosis which were intractable to medical treatment or were complicated by several episodes of severe hemorrhage. Following severance of the vagus nerves to the stomach, Dragstedt⁹ and others^{10, 11, 12} since have reported the immediate relief of pain, gastric hypomotility, delayed emptying time and a reduction in the total night secretion and acid levels. They have stated that most of their patients have remained well without further medical restrictions. In several cases, because of persistence of obstructive phenomena, gastroenterostomy or pyloroplasty had to be performed subsequent to vagotomy.

It might be interesting to present our experiences with vagotomy in the treatment of duodenal, gastric and jejunal ulceration. These cases were operated upon by Percy Klingenstein, Leonard J. Druckerman and myself. The various gastric acidity tests were performed

under the supervision of Franklin Hollander and Vernon Weinstein and the cases were followed postoperatively by members of the surgical staff and by Asher Winkelstein, Chief of the Gastrointestinal Clinic.

Vagotomy has been performed in one hundred and twenty-six cases of duodenal, gastric and jejunal ulcer from December 1, 1945 to February 1, 1948 (Table I). In the first thirty-five patients the supradiaphragmatic approach was employed. This procedure is comparatively simple. It is performed through an incision in the left 8th costal interspace. After incising the overlying parietal pleura, the esophagus is easily mobilized just above the diaphragm where segments of the main vagal trunks and all their interlacing branches may be easily exposed and excised. The mortality in this series was nil. The main and very important objection to the thoracic approach is that no opportunity is afforded for abdominal exploration unless the diaphragm is incised. In the last ninety-three cases infradiaphragmatic vagotomy was performed. This has the distinct advantage that it permits a thorough abdominal exploration. The infradiaphragmatic portion of the esophagus is more fully visualized after the coronary ligament has been divided and the left lobe of the liver has been retracted to the right. The esophagus may be further mobilized by separation from the surrounding tissues after circumferential division of its peritoneal covering. At this stage the vagi may be felt as taut vertical cords, and adequate segments of the nerves may be excised. This procedure is highly satisfactory.

Supradiaphragmatic vagotomy has been performed upon twenty cases of uncomplicated chronic duodenal ulcer, and infradiaphragmatic vagotomy upon one (Table II). The predominating symptom in this group was bleeding in three and recurring attacks of pain in eighteen cases. All patients had received a previous course of medical treatment on more than one occasion. None of these cases were complicated by pyloric stenosis. Following operation all patients were treated by Wangensteen suction for four or more days. All but one of the patients were immediately relieved of pain. Nine patients remained well for periods of nine to twenty months, although seven of these suffered from motility disturbances of gastric atony which lasted from one to fifteen months. Five were improved during the period of observation from nine to sixteen months. In five patients the motility disturbances

TABLE II—22 CASES OF UNCOMPLICATED ULCER
TREATED BY VAGOTOMY ALONE

<i>Surgical Approach</i>	<i>Diagnosis</i>	<i>Predominant Symptom</i>	<i>Results</i>
Supra-diaphragmatic	Duodenal ulcer	3 Bleeding $1\frac{1}{2}$ to 7 yrs. 17 Pain $1\frac{1}{2}$ to 25 yrs.	8 Well—13 to 20 months Motility disturbances in 6, lasting 1 to 15 months 4 Improved—12 to 16 months 8 Unimproved 5 Severe gastric atony Reoperated after 6 to 20 months 3 Recurrent ulcer 2 Reoperated after 2 and 14 months 1 Treated medically 18 months
	20 cases		
	Gastric ulcer 1 case	Pain 4 yrs.	Well—20 months Motility disturbances 5 months
Infra-diaphragmatic	Duodenal ulcer • 1 case	Pain 20 yrs.	Improved—9 months Motility disturbance 2 months

were severe. In this group (Table III) the foul eructations, vomiting and gastric oppression were unrelieved by medical measures and became so intolerable that further surgery was necessary to relieve the gastric stasis. A subtotal gastrectomy was done in four patients in from six to twenty months following the vagotomy. In one other of these cases with a positive insulin test, an unsuspected active duodenal ulcer was found and a subtotal gastrectomy was performed eleven months following operation. Three patients complained of recurrent ulcer pain, and in two in which the insulin test revealed a complete vagotomy, exploration disclosed an active duodenal ulcer. A subtotal gastrectomy was done in both cases. The third case is still receiving medical treatment. From these observations (Table IV) there appears to be no apparent correlation between the completeness of the vagotomy as revealed by the insulin test and the clinical results which were observed. Moreover, at present there seems to be little uniformity in the technique or the interpretation of the insulin test.

TABLE III.—RECURRANCES FOLLOWING SUPRADIAPHRAGMATIC VAGOTOMY FOR DUODENAL ULCER

Case	Preoperative Diagnosis and Symptoms	Date of Vagotomy	Postoperative Symptoms	Date of Abdominal Exploration		Operative Procedure
				12-12-46	12-12-46	
J.R. 547866	Duodenal Ulcer Pain—7 years	5-2-46	Vomiting Foul Fruetions, Pain	Colon and Duodenum	— Dilated Liver Stomach	Exploraton Only
R.H. 548657	Duodenal Ulcer Pain—6 years	5-16-46	Vomiting Foul Fruetions	1-9-47	— Patent Liver Stomach	Exploraton Only
A.J. 548160	Duodenal Ulcer Pain and Vomiting —25 years	5-16-46	Vomiting Foul Fruetions	10-28-46	— Dilated Liver Stomach	Exploraton Only
A.A. 549604	Duodenal Ulcer Pain—1½ years	6-3-46	Vomiting Foul Fruetions Pain	12-2-46	— Healed Liver Stomach	Exploraton Only
W.K. 547493	Duodenal Ulcer Pain—1½ years	5-13-46	Vomiting Pain	7-8-46	— Dilated Liver Stomach	Exploraton Only
A.M. 551369	Duodenal Ulcer Pain—7 years	9-30-46	Pain (after 8 mos.)	11-11-47	— Active Liver-pyloric Stomach	Exploraton Only
N.K. 576350	Duodenal Ulcer Pain—15 years	5-27-46	Vomiting Foul Fruetions	2-3-47	— Active Liver Stomach	Exploraton Only

TABLE IV—ANALYSIS OF 19 CASES OF UNCOMPLICATED DUODENAL ULCER TREATED BY VAGOTOMY ALONE

Post-Vagotomy Insulin Results	Clinical Results		
	Satisfactory		Unsatisfactory
	Severe Gastric atony	Ulceration	
Positive 6 (31%)	2	3	1
Negative 12 (63%)	8	2	2
Equivocal 1 (5%)	1	0	0
Complete Anacidity 0 (0%)	0	0	0
Total 19 (100%)	11	5	3

Although the series is admittedly small, the summary in our experiences in twenty-one cases of uncomplicated chronic duodenal ulcer has convinced us that the results of division of the vagus nerve to the stomach appear to be so inconstant and unpredictable that vagotomy as a sole procedure cannot be offered as a reliable therapeutic measure to patients with chronic duodenal ulcer without obstruction. Other observers have had similar experiences.^{12,13,14} We therefore have discontinued it.

Certainly in cases in which chronic duodenal ulcer is complicated by stenosis, the surgeon opposed in principle to subtotal gastrectomy as a procedure might perform a gastroenterostomy and a complementary infradiaphragmatic vagotomy. Inasmuch as a considerable degree of gastric hypomotility is always present following the severance of the vagi, and since it can never be predicted which case will develop intractable gastric dilatation necessitating months of medical therapy and possibly surgery, would the best interests of these patients be served in routinely combining gastroenterostomy with vagotomy? Some observers have vigorously condemned this viewpoint. The symptoms

TABLE V—DUODENAL ULCER TREATED BY COMBINED PROCEDURES

No. of Cases	Operation	Predominant symptom	Results
26	Gastroenterostomy and Infradiaphragmatic Vagotomy	22 Pain—1½ to 30 years 2 Bleeding—3 to 14 years 2 Obstruction—9 to 12 months	17 Well—6 to 24 months 3 Improved—7 to 10 months 1 Recent 2 Recurrences—8 months and 1 year 2 No follow-up 1 Death
50	Subtotal Gastrectomy plus Infradiaphragmatic Vagotomy	38 Pain—1 to 19 years 12 Bleeding—1 month to 20 years	30 Well—4 to 25 months 7 Improved—6 to 21 months 10 Recent 3 No follow-up

of duodenal ulcer are invariably relieved by gastroenterostomy and the ulcer usually heals. The unfortunate disadvantage of this simple operation is the high incidence of subsequent gastrojejunal ulceration. Perhaps careful follow-up studies over the next five to ten years will demonstrate the efficacy of the added infradiaphragmatic vagotomy in the reduction of the incidence of gastrojejunal ulceration after gastroenterostomy. To date gastroenterostomy with infradiaphragmatic vagotomy has been performed in twenty-six cases (Table V). This combined procedure was done mainly in those considered poor risks for a subtotal gastrectomy, substantially patients advanced in years and others suffering from hypertensive cardiovascular disease, severe diabetes or marked obesity. The majority of the patients were suffering from pain, two from recurring attacks of hematemesis, and two from the effects of an intractable obstruction. There was one death in this group. This patient, 68 years of age, was suffering from an alkalosis incident to a pyloric stenosis. A preliminary jejunostomy for jejunal alimentation was performed. Following this, when her condition had improved, a gastroenterostomy and infradiaphragmatic vagotomy was done. The jejunostomy tube was inadvertently removed four days after operation, and then, because of persistent vomiting due to recurring gastric atony, a second jejunostomy was done. She subsequently died of peritonitis.

The effects of postoperative atony were not as marked as those in which vagotomy alone was done, and these difficulties lasted for a shorter period of time. Seventeen of the patients have remained well from six to twenty-four months, three have improved, one is too recent for evaluation, in two there has been no follow-up. There were two unsatisfactory results. A gastrojejunal ulceration developed in one patient eight months after operation, and in the other a year later. Both patients are being treated medically.

Subtotal gastrectomy of the Billroth II type is still the procedure of choice in patients suffering from chronic duodenal ulcer in this clinic. However, if the mortality is to be kept low, all patients prior to operation must be adequately and carefully prepared. Many patients, especially those who are admitted to the surgical wards of a large metropolitan hospital suffering from the devitalizing effects of recurrent ulceration, are poor risks. Previous dieting, often with inadequate caloric and vitamin intake, and bouts of persistent vomiting, incident to pylorospasm, or stenosis, cause metabolic disturbances resulting in hypoproteinemia, inanition, avitaminosis, dehydration and often alkalosis. Severe hemorrhage or intermittent oozing of blood from an erosion or ulcer crater may induce an acute or chronic anemia with all its implications. These physical alterations and chemical imbalances militate against successful major surgical procedures. The complications of an acute or chronic duodenal ulcer, aside from an acute perforation, should be treated conservatively at first. We do not feel that even massive hemorrhage in patients over forty-five years of age necessarily is an indication for emergency surgery. It is true that occasionally patients bleed to death following conservative medical treatment. However, according to the statistics of Crohn and Lerner¹⁵ the results of such therapy are far better than those obtained by radical emergency surgery. Undoubtedly blood and plasma may effectively increase the red blood count, raise the percentage of hemoglobin, elevate blood pressure and eliminate shock sufficiently so that these patients may be explored. But the impoverished and anemic tissues of the body are slow to recover from the dire effects of a pre-existing anoxemia. Tissue healing is impaired and pulmonary complications are frequent. Consequently the resultant operative mortality is high. In our experience better results are obtained by medical treatment in most acutely bleeding ulcers. Definitive surgery should be performed

at a later period, when most of these patients have recovered fully from the effects of their blood loss.

Most patients suffering from chronic ulcer require adequate hydration and restoration of the electrolytic imbalances by the parenteral administration of glucose and saline. Hypoproteinemia, if present, may be corrected by the oral administration of a high protein diet. If this is impractical because of a pyloric stenosis, blood plasma, blood and amino acids may be given parenterally to elevate the lowered serum proteins. Patients with pyloric stenosis evidenced by marked gastric retention demand special attention. The vomiting has resulted in a loss of chlorides of the gastric juice which are reflected in the lowered chloride content of the blood, and a high CO₂ combining power. Intravenous saline in adequate amounts will correct this alkalosis. In addition, hot gastric lavages will usually relieve the pylorospasm and often allay the local inflammatory reaction to such a degree that eventually gastro-duodenal continuity will be restored. If, in spite of these conservative measures, the gastric dilatation is unrelieved, and the alkalosis becomes increasingly severe, a preliminary jejunostomy for alimentation may be indicated.¹⁶

Spinal anesthesia is selected because it provides excellent relaxation and exposure. Unfortunately it does not eliminate pulmonary complications which still contribute to the mortality and morbidity of gastric operations. In cases in which, because of technical difficulties or physical contraindications, a spinal puncture is impossible or undesirable, cyclopropane supplemented by curare is preferred.

The subtotal gastrectomy performed in our clinic is the Hofmeister modification of the Billroth II type, restoring gastrointestinal continuity by a terminolateral gastrojejunostomy, making the anastomosis anterior to the colon instead of retrocolic. Postoperatively these patients are given parenteral fluids and blood if necessary. Fluids are given by mouth within twenty-four hours and most patients are allowed out of bed on the first or second postoperative day. The indwelling Levin tube is removed as soon as the return of gastric tone is evident. The mortality of this procedure has gradually been reduced,¹⁷ and in the last one hundred and ten cases, from October, 1945 to the present, there have been no deaths.

Follow-up results have revealed instances of the dumping syndrome and recurrent pain and bleeding, symptoms attributable to gastrojejunal

TABLE VI—GASTROJEJUNAL ULCERS

<i>Number and Type</i>	<i>Predominant Symptom</i>	<i>Surgical Procedure</i>	<i>Results</i>
10 Following Gastroenterostomy	4 pain 6 bleeding	2 Supradiaphragmatic vagotomy	1 Well—24 months 1 Recurrence—12 months
		5 Infradiaphragmatic vagotomy alone	5 Well—4 to 10 months
		3 Infradiaphragmatic vagotomy plus subtotal gastrectomy	3 Well—7 to 9 months
17 Following Subtotal Gastrectomy (15 patients)	10 pain 5 bleeding	10 Supradiaphragmatic vagotomy	4 Well—15 to 24 months 2 Improved—24 months *3 Recurrences—10 to 13 months 1 Death
		7 Infradiaphragmatic vagotomy	4 Well—5 to 9 months *2 Recurrences—1 month 1 Recent

* See Case Histories Nos. I and II.

ulceration. While 9 per cent of the patients in one series¹⁸ followed from five to ten years showed clinical evidence of gastrojejunal ulceration, only 3 per cent required further surgery. Recurrences were noted especially in patients who usually had evidences of abundant free acid. Since December, 1945, infradiaphragmatic vagotomy has been added to subtotal gastrectomy in a series of patients. This has been done especially where the preoperative acidity has been high, and those in whom the clinical course had been marked by a tendency to hemorrhage, two categories of cases especially prone to subsequent gastrojejunal ulceration. A series of approximately fifty consecutive cases of duodenal ulcer in which a subtotal gastrectomy was done was compared with a contemporaneous series of fifty cases of duodenal ulcer in which a subtotal gastrectomy was combined with an infradiaphragmatic vagotomy. There was no mortality in either group, and

there was slight difference in the postoperative morbidity. We therefore feel that vagotomy may be added without additional hazard. Whether a comparison of the follow-up results in these two series will reveal any differences in their future course, especially as far as the recurrence of gastrojejunal ulceration is concerned, only time will tell.

Vagotomy has been used in the treatment of twenty-seven cases of gastrojejunal ulcers (Table VI). Ten were done for ulceration following gastroenterostomy and seventeen were incident to subtotal gastrectomy. The surgical procedures formerly used in these cases were extremely difficult technically. The operative mortality was high, especially in the tertiary resection following secondary gastric resections, and even in the survivors, subsequent ulcerations were not infrequent. The immediate results of vagotomy in these cases were striking.¹⁹ The severe agonizing pain was almost instantly relieved. In the majority the free acid was materially reduced in quantity, or an anacidity was produced. The ulcers which were previously demonstrated by x-ray rapidly disappeared. The postoperative course was not complicated by any marked delay in gastric emptying. To date there is one case in which a recurrence of ulceration followed a supradiaphragmatic vagotomy for a jejunal ulcer after gastroenterostomy and there were three recurrences in from ten to fifteen months following vagotomy for jejunal ulcer following subtotal gastrectomy. In none of these cases was the postoperative insulin test negative. The history of two of these cases is briefly presented.

Case 1: E.I., a 55 year old female, had had a subtotal gastrectomy for duodenal ulcer at another institution in May, 1945. A few months later she developed pain and bleeding. X-rays were positive for jejunal ulcer. In February, 1946, a transthoracic bilateral vagotomy was performed. Following this procedure, the ulcer disappeared as evidenced by X-ray taken two weeks after operation. The insulin test was positive. There was marked clinical improvement for six months. However, she began to have recurrent hemorrhages. In April, 1947, the patient was re-explored abdominally, a jejunal ulcer was found and an infradiaphragmatic vagotomy performed. The insulin test remained positive. The patient remained well for one month, at which time hemorrhage recurred. In November, 1947, a third abdominal exploration was performed and a large jejunal ulcer was removed. Further gastric resection was then done to such an extent that only a small portion of the

stomach remained. Postoperative histamine test revealed no free acid. The patient has since been well.

Case 2: M.E., a 52 year old female, had had a subtotal gastrectomy for duodenal ulcer performed at another institution in December, 1945. Within a week after that operation, the patient had recurrence of pain which subsequently was proven by X-ray to be due to jejunal ulcer. In May, 1946, a transthoracic bilateral vagotomy was done. There was immediate and dramatic relief of pain. X-rays taken two weeks later showed marked diminution in the size of the ulcer. The postoperative insulin test was positive. However, five months later the pain recurred with such severity that exploration was necessary. Accordingly in June, 1947, laparotomy was performed and a large jejunal ulcer was found. A right posterior vagus nerve trunk was found and excised. The left anterior was represented only by a few fibrous strands which were divided. There was no relief following this operation. The insulin test remained positive and X-rays taken four months later again demonstrated the jejunal ulcer. The pain was intractable and a third abdominal exploration was performed in November, 1947, at which time a large jejunal ulcer and an additional portion of the stomach were resected. Postoperatively, free acid was present with the histamine test despite an extremely high gastric resection. The patient has been well since this last operation.

It will be noted in both these cases, following supradiaphragmatic vagotomy the ulcers disappeared by x-ray and patients were well clinically for a short period. Following an infradiaphragmatic vagotomy at a later date the same sequence of events occurred, only the interval of well-being was of shorter duration. In these two cases great care was taken to divide all vestiges of the vagus nerve, at first above, and then later below the diaphragm. Yet in spite of this the insulin test remained positive. It would seem reasonable from this evidence to assume that vagal nerve fibers are transmitted by channels other than those grossly visible anatomically, i.e., either through the wall of the esophagus to the plexuses of Meissner and Auerbach in the stomach, or possibly by parasympathetic fibers in the gastric sympathetic nerves. Because of these recurrences following vagotomy we now feel that patients suffering from jejunal ulcer following gastroenterostomy, provided that they are good operative risks, should be subjected to radical surgery in which the gastroenteric stoma should be disengaged, the

jejunal ulcer excised, and a high gastric resection should be done combined with an infradiaphragmatic vagotomy. If practical, in recurrent ulceration following subtotal gastrectomy, an abdominal exploration should be done, a resection of the ulcer performed, and as much of the gastric mucous membrane resected as is possible, combined with infradiaphragmatic vagotomy. If these patients are in poor physical condition, an infradiaphragmatic vagotomy as a sole procedure should be tried.

It will be noted that there was only one case of gastric ulcer treated by vagotomy (Table II). While there may be no unanimity of opinion as to the surgical treatment of duodenal ulcer, the question of surgery in gastric ulcer no longer presents a problem. It is almost universally agreed now that subtotal gastrectomy is indicated in most of these cases. The differentiation between benign and malignant ulcers of the stomach may offer great difficulties. The fact that the ulcer grows smaller as evidenced by x-ray examination following a course of medical therapy does not necessarily mean that the lesion is benign. While it is true that a benign ulcer rarely undergoes malignant transformation, it does occasionally occur. Gastroscopic examination has been of inestimable value in distinguishing between benign and malignant ulcers, but it has not entirely eliminated this diagnostic error. Even many excised gastric ulcers which according to all criteria were considered to be grossly benign have been proven malignant by subsequent pathologic examination. If all these factors were borne in mind, there should be less hesitancy on the part of the profession in subjecting gastric ulcers to radical surgery. The results of subtotal gastrectomy for these lesions have been excellent, and inasmuch as most of the cases develop a postoperative anacidity, recurrent gastric or jejunal ulcer is extremely rare. In the past nine years, in a series of consecutive cases of gastric ulcer in which subtotal gastrectomy was the only procedure which was performed, the mortality was reduced to 6.5 per cent.²⁰ This reduction was due to the fact that cases with hemorrhages were rarely operated upon during the acute phase and that ulcers high on the lesser curvature, juxtaesophageal, were not excised. There was only one case operated upon during an acute episode of hemorrhage. In nine cases in which the ulcer was so close to the region of the esophagus that in order to remove it a total gastrectomy may have been necessary, a "palliative" gastric resection was done. In this procedure

the ulcer is left in situ, provided that examination of the lesion and a frozen section if necessary determines its benignity. The stomach distal to the lesion is then removed and gastrointestinal continuity is restored. The gastric ulcer subsequently disappears according to roentgen and gastroscopic examination, and the patients have remained well for years.

We therefore feel that because of the excellent results produced by gastric resection, vagotomy has no place in the therapy of gastric ulcer.

SUMMARY AND CONCLUSIONS

1. Vagotomy as a sole procedure has been abandoned in the treatment of unobstructed duodenal ulcer as a result of our experiences in a series of twenty-one cases, because seven of them required further surgery, two for recurrent duodenal ulcer, and five for gastric dilatation and atony. The completeness of the division of the vagi as evidenced by the insulin test bears no relationship to the clinical results.

2. The addition of gastroenterostomy to vagotomy seems to have eliminated the undesirable effects of gastric atony in twenty-six cases of duodenal ulcer in which it was performed. Whether the incidence of gastrojejunal ulceration will be lessened by the combination of vagotomy and gastroenterostomy, as compared to gastroenterostomy alone, only long range follow-up studies will determine.

3. Gastroenterostomy combined with bilateral infradiaphragmatic vagotomy is the preferred procedure in cases of duodenal ulcer unsuitable for subtotal gastrectomy.

4. Subtotal gastrectomy still remains the operation of choice in duodenal ulcer. It has been combined with infradiaphragmatic vagotomy in a series of patients whose pre-operative acidity was high, and who had a tendency to bleed. There has been no increase in the operative mortality and a slight increase in the postoperative morbidity attributable to the added vagotomy. Whether the incidence of recurrent gastrojejunal ulceration will be diminished remains a subject for further study.

5. The immediate results of vagotomy in the treatment of gastrojejunal ulceration following gastroenterostomy and subtotal gastrectomy have been excellent. Subsequent follow-up has revealed recurrent ulceration in some cases. In patients considered to be good operative risks, a subtotal gastrectomy with infradiaphragmatic vagotomy is preferable to vagotomy alone for gastrojejunal ulceration following

gastroenterostomy. In gastrojejunal ulceration following subtotal gastrectomy, wherever possible resection of the ulcer and further gastric resection combined with infradiaphragmatic vagotomy would seem preferable to the severance of the vagus nerves alone.

6. Vagotomy is not indicated in the treatment of gastric ulcer.

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THE HISTORY OF NEUROLOGY IN THE LAST ONE HUNDRED YEARS*

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NEUROLOGY may be considered from differing viewpoints, for in its broadest aspects neuroanatomy, neurophysiology, neuropathology, neurosurgery and clinical neurology are integral parts of the larger concept. One might, with some justification, even include psychiatry, a disease of the nervous system, and therefore within the dictionary definition of neurology as "the scientific study or knowledge of the anatomy, functions, and diseases of the nerves and the nervous system."¹ But such an encyclopedic designation reverts to the late seventeenth century and is not applicable to the nineteenth, when specialization was beginning and the neurologist was no longer primarily concerned with anatomy and physiology, his main efforts being directed to disease and injury as they affected the nervous system of man. The term neurologist indeed dates from 1832, the year that Romberg introduced the work of Sir Charles Bell to his Berlin audience. By circumscribing its field of activity neurology did not by any means lose contact with anatomy or physiology. The best in modern neurology has developed hand in hand with the basic sciences as witnessed by the work of Cajal and Sherrington in the laboratories, Charcot and Cushing in the clinic. Thus, although we should not delimit our subject in general, time only permits a brief review of the clinical aspects of neurology in the last one hundred years and a survey of the leaders who made the most significant contributions. Should you desire to go further you will find that other and more able hands have penetrated deeply into the subject of the growth of our specialty. I refer to the well-documented "History of Neurology," by Fielding H. Garrison;² "Fifty Years of American Neurology," by Smith Ely Jelliffe;³ the "Introduction to the History of Neurology," by Israel S. Wechsler⁴ and the many important papers

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in the *Foundation Volume Published for the Staff, to commemorate the Opening of the Montreal Neurological Institute, of McGill University, 1936.*⁵

Moritz Heinrich Romberg (1795-1873): The growth of clinical neurology as a specialty is almost exactly one hundred years old for Romberg was the first physician to give particular attention to the structural diseases of the nervous system, and neurology as we know it today, in practice and in the clinic, developed only after he published the first edition of his *Lehrbuch der Nervenkrankheiten*,⁶ the first volume in 1840 and a final one in 1846. The book, unique in content, soon passed into a second and later a third edition.

Born in 1795, Romberg had completed his usual medical studies at the age of 22 when he selected the study of the diseases of the nervous system as the object of his life and the goal of his researches. He was much influenced by English authors and one of his first duties as a young man was to translate into German⁷ a book by the London anatomist, Andrew Marshal, on *The Morbid Anatomy of the Brain, in Mania and Hydrocephalus*.⁸ Marshal, born in Scotland, had become a pupil of William Hunter in Great Windmill Street, London, where John Hunter was also lecturing on surgery. He practiced medicine in London and lectured on anatomy. The book that Romberg chose to translate was published in 1815, two years after Marshal's death, edited by Dr. Sawrey, his former assistant lecturer. Marshal's chief activities were concerned with his school of anatomy in the Thavies Inn in London and in the practice of medicine. Marshal described the gross appearance of the brains of patients who had died of mania at the Bethlem Hospital and proved to his own satisfaction that the structure of the brain was always grossly altered, due, in his opinion, to defective circulation. He found fluid in the cerebral ventricles and erroneously interpreted this as a sign of disease. The book does not seem to be of any considerable importance at the present time but perhaps it stirred the young Romberg on to better things and, at least, it introduced him to contemporary English neuroanatomy and neuropathology. He was thus led to the work of Sir Charles Bell who became his guide in neurological research.

Of more importance, therefore was his translation of Bell's *The Nervous System of the Human Body*, which had appeared in London in 1830 and was promptly put into German by Romberg in 1832, with

the fine plate showing the trigeminal, facial and vagus nerves.⁹ This was a much more noteworthy contribution than the book by Marshal, for it brought to the German-speaking world one of the great landmarks in neurology. Romberg was conscious of this for he states, "the researches of Sir Charles Bell fill me with enthusiasm, and in 1831 I translated his great work and made known to my professional brethren in Germany his investigations which will ever serve as models of scientific inquiry." In this book Bell demonstrated the motor and sensory character of the trigeminal nerve and separated it from the facial nerve with which it had previously been confused.

The value of Romberg's translations and his demonstrated interest in diseases of the nervous system was soon recognized and he was invited to lecture on neurology at the University of Berlin as early as 1834. In 1840 he was appointed director of the wards of the University Hospital and there he began his studies of patients, observations that were recorded in various editions of his famous textbook, then in the course of preparation.

The discovery of the motor function of the anterior root by Sir Charles Bell in 1811, the elucidation, with experimental proof, of the functions of both the anterior and posterior roots by Magendie in 1822 and the acceptance of the difference between sensory and motor nerves by Bell in 1826, led to a division of Romberg's textbook into two sections, one on sensation and the other on motion. In the sensory section there are excellent descriptions of neuritis, causalgia, neuromas, facial neuralgia, ciliary neuralgia, sciatica, and many other conditions which we recognize today, each clearly illustrated by case histories and with full references to the literature. The section on motor disease is largely given over to a description of muscular spasm, particularly those concerned with breathing and talking. The space given to this would seem inordinately large according to present day standards. Later in the same volume are found descriptions of chorea, tetanus, epilepsy, facial paralysis, and finally tabes dorsalis, with a note on the famous sign which goes by Romberg's name. Romberg does not clearly differentiate spinal from peripheral nerve disease and classified lead poisoning among the diseases of the spine. There are various examples of intrinsic degenerative disease of the spinal cord but the differentiation of these was left for others.

Romberg's description of tabes dorsalis discloses his great power of

observation. For example, the sensory alterations in tabes dorsalis are thus recorded: "The feet feel numb standing, walking, or lying down and the patient has the sensation as if they were covered with fur. The resistance of the ground is not felt as usual; its cohesion seems diminished and the patient has the sensation as if the sole of his foot were in contact with wool, soft sand or a platter filled with water. The rider no longer feels the resistance of the stirrup and has the strap put up a hole or two." This was no theorizing. Romberg was actually talking in terms of patients he had examined and for the first time in a consecutive orderly manner under the covers of one book we begin to get a clear picture of clinical neurology.

The text of Romberg's book was not translated into English as rapidly as Romberg had translated Bell's treatise in German, for it was not until after the second German edition of 1851 that an English edition was issued in London in 1853.¹⁰ The rendition, however, was excellent and the volumes had a wide influence not only in Great Britain, but also in America.

The original idea for the book came from Romberg's admired predecessor, Sir Charles Bell, who wrote, in 1811: "I fear it will be a long time before combined efforts will enable a medical author to arrange and accurately describe the diseases of the nervous system. The position we at present occupy is but a very inferior one." Romberg did not forget these words, and by 1840 the first part of his book was ready for the press. The text was based on physiological principles, for Romberg examined the literature of his day with great completeness. He collected and incorporated the scattered reports on experimental investigations into his precise clinical pictures of neurologic diseases.

Romberg's fame not only rests on his textbooks but on his superb definition of the clinical aspects of tabes dorsalis and his brilliant pathological surmise, based on direct observations, "that the posterior sensory roots are occasionally alone affected in conjunction with the posterior of the spinal cord, the anterior motor column and nerve retaining their normal structure." Although many of the clinical symptoms had been noted by others, Romberg, using the observations of others and those of his own, wrote the classical description of the disease. For this he deserves enduring fame.

Duchenne de Boulogne (1806-1875): Guillaume-Benjamin-Amant

Duchenne, the strangest figure that ever entered the field of neurology, labored under a great disadvantage, for he cared little for book knowledge and knew nothing in his early and most productive days of the work of Romberg and his other contemporaries. He therefore started his clinical career by himself and continued as a solitary investigator during his entire life. Such isolation might be considered a handicap to an ordinary man, but Duchenne was far from orthodox. The results of his solitary studies were so outstanding that we may agree with Joseph Collins' clever characterization: he found neurology "a sprawling infant of unknown parentage which he succored to a lusty youth."¹¹

Duchenne, a strong fisherman type from Boulogne, had no hospital appointment in Paris and sought none. Typically a man devoted to bedside observations, he never expended his energies on lecturing. Duchenne had no special talent for the pursuit of morbid histology, although he was one of the first to use photography as a means of preserving microscopic pictures. Going from hospital to hospital, ever talking to and examining patients, this persistent investigator even followed patients into their homes. At first he was received with considerable skepticism by the medical profession of Paris but slowly his reputation and his superiority in clinical observation was soon widely accepted. Duchenne finally became known as an honest, hard working original discoverer, a skillful professional man and a kind-hearted benevolent gentleman.¹²

Duchenne's first book of importance, published in 1855, was *De l'électrisation localisée*.¹³ There was a second edition in 1861 and a third in 1872. His clinical observations were not only published in the medical journals of the day but gradually added to the various editions of his book on electrotherapy. The first edition contained almost no clinical observations but when the third was published in 1872 the bulk of the clinical work of Duchenne was incorporated into this work. All editions contain his work on electrical stimulation of the muscle, the elucidation of the mechanism of facial expression and the complete review of muscular function as depicted by stimulation of the muscle itself. The third edition of this book is the one most useful to the clinician. The first part reached England in 1870 before the German army had entered Paris. This was promptly translated¹⁴ and came out before the third French edition. The clinical works, contained in the second part, were not issued in English until 1883.¹⁵

Duchenne's contribution to neurology is signalized by his clinical descriptions of progressive muscular atrophy, poliomyelitis, tabes dorsalis, glossolabiolaryngeal paralysis and pseudo-hypertrophic paralysis. These observations cannot be said to be entirely original with Duchenne but their value lies in the fact that Duchenne put together into clinical entities the various aspects of the diseases under consideration. This is particularly true in tabes, which he called progressive locomotor ataxia, thus improving the somewhat unfortunate name, tabes dorsalis, given to it by Romberg. Duchenne added to Romberg's description of the symptoms; indeed he made his word picture so complete that hardly anything has been added to it since his day except the joint and bone manifestations, the trophic disturbances and, of course, the absence of the deep reflexes and the pupillary abnormalities. These were supplied at a later period by Charcot, by Westphal and by Argyll-Robertson. Duchenne, moreover, described some of the earliest symptoms of the disease. There was always some doubt in his mind whether the disease as noted by him was the same as the advanced tabes dorsalis described by Romberg.

Duchenne also described fully and accurately the symptoms and signs of progressive muscular atrophy. He studied the pathology of the atrophic muscles, pointing out the fatty changes that he thought characteristic of the most common form. He also noticed the atrophy of the cells in the anterior horn but he was never sure whether the cord lesions were primary or secondary. It was left to Charcot, with his better apparatus, to solve this problem. Of more importance is Duchenne's fine demonstration of the atrophy of the anterior horn in poliomyelitis. He paralleled his observational studies in the hospital with pathological studies of the spinal cord tissue.

These are Duchenne's chief contributions to neurology but he made lesser additions, particularly in his clinical descriptions of diphtheritic paralysis, the hysterical states, contractures of the diaphragm and peripheral nerve injuries. He studied the mechanism of expression by electrical stimulation of muscles and developed ingenious prosthetic devices for injured hands.

Duchenne, by constant probing at the bedside for thirty years, described clearly for the first time a number of important neurological diseases. We are all indebted to this extraordinary man whose devotion to neurology should never be forgotten. He, even more than Romberg,

stimulated the development of our specialty, for he initiated the great school of French neurology on which so many of our present concepts of neurological diseases are based.¹⁶ Without his two great friends in Paris, Trousseau and Charcot, however, much of Duchenne's work would never have reached publication, for he was absentminded and inarticulate in the public expression of his ideas. Charcot, one of the most eminent practicing physicians of his time and a greater neurologist than Duchenne, was not, however, unmindful of Duchenne's accomplishments and was ever ready to help him make his discoveries known.

Jean-Martin Charcot (1825-1893): The greatest neurologist of all time, Charcot's name will always be associated with his old hospital in Paris, the Salpêtrière. The hospital got its queer name from the fact that it once served as an arsenal and thus became a center for the storage of saltpeter, the essential ingredient of gunpowder. Sometime in the 17th Century it was converted into an asylum for old women and later, after Pinel's time, into a hospital for the mentally disturbed, epileptics and patients with a wide variety of nervous diseases. To this hospital in 1848 came the young Charcot as a medical student, the son of a professional carriage builder who had considerable artistic talent, an inheritance that became well marked in his famous son. As a boy the young Charcot had become proficient in at least three languages besides French: English, Italian and Dutch. After four years of internship at the Salpêtrière, Charcot practiced medicine for a few years before returning in 1862 to his old hospital as one of the chiefs of the medical service. His early work, indeed, was in general medicine, studies on gout, rheumatism, diseases of the heart, lungs, liver and kidneys and particularly the delineation of the pathological condition associated with old age. One of his first concerns was to establish a pathology laboratory at the Salpêtrière. From a single small room granted him for this purpose came some of the greatest discoveries ever made in neuropathology. Charcot began at the very onset of his career, unlike his friend Duchenne, to examine the tissues of the nervous system. His elucidation of the morbid changes associated with the clinical states that he saw in the wards, proceeded in rapid succession. He demonstrated the changes in the anterior horn cell in poliomyelitis, already noted by Duchenne, and in progressive muscular atrophy; then came the studies on miliary aneurysm and the role it played in the causation of cerebral hemorrhage and finally his work on cerebral hemorrhage

itself and softening of the brain. In addition, he delineated clinical aspects of tabes dorsalis improving greatly on the descriptions of his predecessors and for the first time, described the gastric crises and the arthropies. There followed a long and detailed study on tremors in which he dissociated the tremor of paralysis agitans from that of multiple sclerosis and put tremor, which had hitherto been regarded as a disease, into the status of a symptom. He demonstrated the plaques in multiple sclerosis and clearly set forth the clinical aspects of this disease. Charcot described accurately the pathological changes in the spinal cord in amyotrophic lateral sclerosis and indicated the chief symptoms in the peroneal type of muscular atrophy. His crowning achievement in neuropathology was his studies in cerebral localization. Basing his work on the animal experiments of Hitzig in Germany and those of Ferrier in England, Charcot delineated the pre-rolandic cortex, the internal capsule and particularly the blood supply of the capsule itself.

Such were the fundamental studies that came out of the pathology laboratory established at the Salpêtrière in 1862. His name is remembered in the artery of Charcot, Charcot's disease, amyotrophic lateral sclerosis and the changes in the joints in tabes dorsalis. Although his reputation as a teacher in part is associated with his demonstrations of the psychoneuroses, from the point of view of neurology, he must be considered as the greatest contributor to our knowledge of structural disease of the nervous system. Charcot was a man of great personal charm, an ardent student of literature, an artist of distinction, a man of great intelligence and industry. He was, indeed, the founder of modern neurology and his studies in cerebral localization led directly to the development of neurosurgery.

Many memoirs have been written about Charcot. One of the best, based on personal observations, is by Allen Starr, read before the New York Neurological Society the year of Charcot's death, 1893.¹⁷ A more extensive and critical account was given by F. H. Garrison at the time of the Charcot Centenary in 1925.¹⁸

John Hughlings Jackson (1835-1911): Like Duchenne, Hughlings Jackson was a clinical neurologist. Never an experimentalist, he sought his facts in the patient and integrated those facts into broad concepts of disease. He allowed the experiments to be made by nature and studied their results on the nervous system of man. The son of a Yorkshire farmer, Jackson qualified as a physician in 1866 at the St.

Bartholomew's Hospital in London about the time that Charcot was finishing his internship at the Salpêtrière in Paris. He almost decided to go into philosophy but Jonathan Hutchinson persuaded him to come up to London from York, where he had settled after qualifying as a physician. His chief hospitals in London were Queen Square and the Moorfields Eye Hospital. It was at the latter institution that he first became interested in the ocular changes associated with disease of the nervous system and he introduced the ophthalmoscope to neurology. His methods of work were something like those of Duchenne. He made careful observations, tabulated all the facts, put them into their proper perspective, but finally went further than Duchenne in the generalization of principles. He wrote over three hundred papers that covered an enormous field of reports of individual cases, pathological investigations and physiological studies. A philosophical trend is evident in most of his papers; some are dull and ponderous, but the facts are clear and from them are built up reasoned principles based on sound logic.

Jackson contributed three important concepts to neurological thought: the type of epilepsy that goes by his name, his theory of aphasia and his doctrine levels of function of the nervous system.

His studies on epilepsy began early in his career, about 1865, and continued into the twentieth century. The conception of focal seizures came to Jackson slowly and was not published in its full form until 1874-76. In his studies on speech defects he recognized the previous work of Broca on localization. His chief contribution to the complex question of aphasia was his insistence that mental images may be unaffected in the majority of cases.¹⁹ Later in his life Jackson developed his hypothesis of "levels" (spino-medullary, cortical and prefrontal), based on the observation that the evolution of the nervous system is from the simple to the complex. In nervous diseases the opposite is seen, for the highest and most complex functions are often the first to disappear, leaving the simple and lower level functions in evidence. As a corollary to this, Jackson established that negative or destructive lesions do not produce positive symptoms; these are the outcome of the action of normal structures, acting without the control or restraint of the more highly developed structures of the higher levels.²⁰

Much of his work, owing to the language in which it is written with a heavy philosophical tinge, was lost to his contemporaries. But, as Sherrington wrote: "Compact in Hughlings Jackson was a fine vein

of pithy thought and phrase. Among its memorable examples stands that figure of the nerve centres as rising in three tiers or levels. It gained common usage, and is witness to its author not least in the tacit and complete assurance that neural organization and coordination are inseparably one."²¹

Some of Jackson's most important contributions appeared in obscure medical journals and it was not until his papers were collected and analyzed that his real contributions were incorporated into neurological thoughts.²² He stimulated a brilliant group of students; among them may be mentioned Henry Head, Gordon Holmes, James Collier, Kinnyer Wilson, Edwin Bramwell, Risien Russel, James Taylor and others, all familiar to neurologists of the present generation.

Wilhelm Heinrich Erb (1840-1921): Quite different from Hughlings Jackson or Charcot was the most brilliant clinical neurologist of the latter part of the nineteenth century, Wilhelm Erb. Born in 1840, the son of an obscure woodsman, Erb began his medical studies at Heidelberg where he became a serious hard working student, first in the field of pathology and internal medicine and later in clinical neurology. It was Friedreich in 1867 who gave him the stimulus to become a neurologist and his first work was on the pathology of peripheral paralysis, a subject that remained of greatest interest to him throughout his life. Within ten years he had published two important books, one on the diseases of the peripheral nerves and another on diseases of the spinal cord and medulla. Stimulated by the work of Duchenne, he became interested in the diagnostic and therapeutic aspects of electricity, and described the reaction of degeneration that now goes by his name. His work in this field resulted in a book on *Electrotherapy*, published in 1882. He was carried too far into this aspect of neurology but he made greater and more fundamental contributions in his study of the muscular atrophies and dystrophies, defined myasthenia gravis and the juvenile form of progressive muscular atrophy. He was quick to recognize the relationship between tabes dorsalis and syphilis, pointing this out to Nonne, who was his assistant, as early as 1885, twenty years before the discovery of Schaudinn and Wassermann. Erb, with Schultze, founded the *Deutsche Zeitschrift für Nervenheilkunde* in 1891 and became the first president of the German Neurological Association.

Perhaps his greatest gift to neurology was in the field of teaching,

for it is to Erb we owe the development of an orderly and systematic manner of examination, so fundamental to diagnosis. He pointed out, too, the importance of the changes in the reflexes as a sign of disease. He succeeded, moreover, in making neurological instruction an integral part of the medical curriculum at Heidelberg.²³

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On this occasion we have thus considered only five figures, Romberg, Duchenne, Charcot, Jackson and Erb, in our review of neurology of the last one hundred years. These men influenced neurology the most, but no one would minimize the impact of neurological thought of their colleagues and pupils—Trousseau, Marie, Dejerine, Babinski and Guillain; Goldflam, Strümpell and Oppenheim; Allbutt, Gowers, Head, Holmes and Horsley; W. A. Hammond, Weir Mitchell, Keen, Dercum, Sachs, Putnam, Dana, Cushing and Jelliffe. Nor can we overlook the influence of Bernard, Pavlov and Sherrington in physiology; Nissl, Alzheimer, Golgi and Cajal in neuroanatomy; Quincke, Röntgen, Ehrlich, Cannon, Langley, von Economo, Dandy, Berger, Ayer, Thomsen, Froin, Forestier, and a host of others who make our daily hospital and consulting room life possible. The advance of knowledge in neurology, as in other disciplines, is mainly the result of individual effort. Great discoveries often are arrived at under conditions far from ideal. Charcot's little room for pathological study, Oppenheim's small desk where he wrote the greatest of neurological textbooks and Duchenne's dreary ward visits were the starting points of momentous advancements. May we take notice and so do our daily tasks, under whatever environment that God put us, so that we may be worthy successors to our forebears, a few of whose names have served to inspire us on this centennial anniversary.

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RECENT ADVANCES IN OUR KNOWLEDGE OF THE CONTAGIOUS DISEASES OF CHILDHOOD*

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OUR entire attitude toward contagious diseases is undergoing radical change. The advent of prophylactic injections was the first factor that influenced us. Next came the specific antisera used in treating disease and finally the discovery of chemotherapy, the antibiotics and the fractionization of plasma. These completely revolutionized our therapy. The result of all these discoveries has been to rob the contagious diseases in great measure of the terror in which they were formerly held. It is my purpose today to review briefly these advances in our knowledge of the common contagious diseases which have made possible such a revolutionary attitude toward their treatment. I shall take up in order, the newer developments in our understanding of scarlet fever, pertussis, mumps, rubella and measles.

SCARLET FEVER

Our first important advance in our handling of scarlet fever was the discovery of the Dick test and scarlet fever antitoxin. With the help of the test and the possibility of conferring passive immunity, a great step forward was made. The use of repeated injections of toxin to produce active immunity is known to you all. The great difficulty in the use of the antitoxin for therapeutic purposes was the frequency with which we encountered severe serum reactions. These unpleasant and sometimes dangerous sequelae made most of us hesitate to use antitoxin except in the severe cases. Along about this time it was found that convalescent human serum was of great value although in the laboratory it was shown to be devoid of high antibody content. Most of you will recall the Convalescent Serum Center established at the Willard Parker

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Hospital when human serum was obtainable both for measles and scarlet fever. I myself had great faith in the convalescent scarlet serum and saw some very brilliant results with its use. Its great value was that it could be administered intravenously without reactions. With the advent of the sulfa drugs, another potent weapon was put at our disposal. At the same time serologists and chemists refined the scarlet antitoxin so that after its injection, severe reactions were much less likely to occur. The next development was the discovery of penicillin which proved so useful in streptococcus disease and last came the discovery of the high content of antibody in the gamma globulin of human blood and its availability as a result of the collection of enormous amounts of blood during the war. This series of discoveries is an imposing one and as you know, has completely changed our attitude toward scarlet fever and its complications. One of the results has been that human convalescent serum is no longer obtainable here in New York since it was considered unnecessary in view of the many other substances now at our command.

A comprehensive and as yet unpublished series of cases has been studied by John Landon¹ of this city. He has compared the results obtained by treating scarlet fever with antitoxin, with penicillin and with gamma globulin. In two papers which are about to appear in print, his results show that gamma globulin given early in the disease in doses of 40-60 cc. is the most effective of these remedies in the prevention of early and late complications of scarlet fever. He also emphasizes what I believe is a very important fact. It has been customary in mild cases of the disease to use only symptomatic treatment, reserving specific therapy such as antitoxin, penicillin or globulin for the moderately or very severe cases. From follow-up investigations it appears that this is not the proper way to handle this disease, since in the mild cases treated symptomatically, sequelae were not uncommon, whereas, when the mild cases were given specific treatment, sequelae were prevented. From Landon's results it would seem advisable, then, to use either penicillin or antitoxin, or globulin, if available, for every case of scarlet fever.

PERTUSSIS

To the layman whooping cough is a disease to be dreaded because of its long duration and the great discomfort suffered by the patient. The average physician thinks of it in more or less the same manner. It is, how-

ever, an extremely serious disease, especially as regards those attacked during infancy. The realization of this fact may be brought home to the physician in two ways, first, by a survey of the vital statistics published by the government and second, by being connected either as a resident or an attending physician in a whooping cough ward of a large contagious disease hospital. As we shall see, pertussis is being robbed of some of its terrors by recent advances in therapy, but unless the greatest care is taken, the mortality among infants is still high. About thirty years ago, before we had vaccines, serums, chemotherapy or antibiotics, I was connected with the Willard Parker Hospital and can remember the feeling of despair and almost horror when it became my turn to take charge of the whooping cough ward. Here young infants would be admitted with pneumonia, or would acquire pneumonia in the hospital, when a fatal outcome was almost a certainty. As we will see, this mortality and morbidity have been tremendously reduced by advances in our knowledge of the diagnosis, prophylaxis and therapy of this disease. Let us first take up the question of diagnosis.

Until a few years ago, there was still doubt as to the actual etiology of pertussis, but it is now well-established that the bacillus discovered by Bordet and Gengou, and now known as *Hemophilus pertussis* is the etiological agent. The presence of this organism in the respiratory secretion of a coughing child should settle the diagnosis. The culture may be made by swabbing the nasopharynx or by a cough plate. A marked lymphocytosis, at times accompanied by hyperleukocytosis, may also prove valuable. However, as you know, both these tests may fail us, and the diagnosis must then be made on clinical grounds.

For a number of years work has been in progress on skin tests for pertussis, various fractions of the bacilli or their products having been used, but until quite recently the results have not been satisfactory. About a year ago, however, two articles appeared from Philadelphia, which give a very promising outlook. In December 1946 under the title of "Institutional experiences with the pertussis agglutinogen as skin test reagent," Felton and Flosdorf² report on a test which they have used for eight years. They studied its use in institutions. All secondary cases of whooping cough occurred in children whose skin tests indicated susceptibility or weak immunity. They also demonstrated the value of the test as a "recall" dose, i.e., a "booster," as shown by the small number of cases following testing of the entire institution popu-

lation. In one institution in which one case of whooping cough appeared, all secondary cases occurred in children who had negative skin tests. The test substance has been improved, as reported in the same journal where Felton, Smolens and Mudd³ describe the clinical standardization of the reagent. It is an acid extracted agglutinogen of phase I *Hemophilus pertussis* which was found to be more potent and to give a more clear-cut reaction which could be read after twenty-four hours. To quote the authors, "The use of agglutinogen has a definite place as a public health measure in periodic examinations of young children. The duration of primary immunization may be determined while the antigenicity of agglutinogen produces a prompt recall of any existing antibacterial immunity." Sauer and Markley⁴ tested the immunity to pertussis by the Flosdorf test, comparing it with complement fixation in a group of about 300 children. They found the skin test positive in 85 per cent compared with 71 per cent positive complement fixation tests. Thus the skin test may reveal a lower degree of immunity than the 3 or 4 plus complement fixation test. The authors suggest that a stimulating dose of vaccine is indicated when the skin test shows an induration of 10 mm. or less. If these results are corroborated and we possess a simple reliable skin test for determining susceptibility to pertussis, it will go a long way to help us in our fight against this disease.

The prophylaxis of whooping cough is another subject which has gone through many changes in the past decade. It is still not completely settled. If the skin test just mentioned is reliable, we will at least have a definite measure of the presence or absence of immunity after vaccination. Until now investigators have used the complement fixation test, the opsonophagic index and the agglutinin titer. The last has been most often employed. In February 1947 DeGara and Mayer⁵ reported on the agglutinative reaction for *Hemophilus pertussis* following whooping cough and following immunization. The reaction was found to be positive in 34 per cent of children who had had pertussis. Following prophylaxis with vaccine, agglutinins were found in 93 per cent—some of the determinations being made as long as nine years after the injections. Stimulating doses of vaccine evoked a marked rise in agglutinins in 97 per cent of the cases. On the other hand, of 17 control untreated cases, 16 had no agglutinins and one showed a low titer. This test has been used by many investigators and from the literature seems to be the most useful of the serological methods.

The most satisfactory antigen used for prophylactic injections to bring about active immunity is a vaccine made from whole *Hemophilus pertussis* bacilli. Dow,⁶ as long ago as 1940, compared the value of such vaccine with products in use at the time and still used by the profession, such as Topagen, U.B.A. and others. Dow found that the vaccine made from whole bacilli was definitely superior to the other products in protecting mice. As Lapin⁷ says, "These products have had their day." For active immunization we should use whole vaccine.

The next question is at what age the injections should be given. Until quite recently it was believed that very young infants could not produce antibodies and therefore prophylactic inoculations were not begun until the 6th or 7th month of life. However, opinions have changed and it has been shown that even very young infants may show antibody response. Waddell and L'Engle⁸ set out to observe immune response by studying the agglutinating titers at different age levels. They injected infants at one week of age, a second dose at one month and a third at three months. They got good results. The agglutinative titers of twenty-two unvaccinated infants one week old showed that one could not expect naturally transmitted immunity. The reactions in very young infants were negligible—less than those found in older infants. They advise immunization at the age of two months.

Sako and others⁹ in New Orleans also carried out a large series of vaccine injections in the very young. A large number of infants (3,793) were inoculated at monthly intervals with 3 doses, beginning at 1-2 months of age. They used the rapid agglutination test and obtained satisfactory results, 75 per cent showing antibody response. They also comment on the fact that young infants tolerate the procedure very well. Adams and his co-workers¹⁰ in Minneapolis have also recently shown that the agglutinin titer of very young infants may be rapidly increased by *weekly* injections of pertussis vaccine. They advocate very early inoculation so as to protect the infant at an age when the disease is fraught with most danger. Though contrary to what we had previously believed, the agglutinin titer rose rapidly and in some infants reached levels as high as 1:1280 but the immunity is not maintained for a long period of time. Immunity persists much longer when the intervals between the injections are increased to a month. Lapin,¹¹ here in New York, disagrees with the use of vaccine at so early an age. He used large doses but found that only 40 per cent of infants injected under six

months were positive, whereas, of those injected after six months, 90-95 per cent were positive. He also comments on the fact that agglutinins, complement fixing bodies and opsonins are not necessarily evidence of protection, but that one will have to test the efficacy of attempts at protection by waiting several years and following the children themselves.

Authorities therefore do not yet agree as to the best time for injection. It would appear to me that since the greatest mortality of the disease occurs in the very young infant, we should attempt to protect as early as possible and since we now know that antibodies may be formed in early life, I believe the proper time to vaccinate is in the beginning of the second trimester.

What type of vaccine should we use? We have the choice of plain, alum precipitated or aluminum hydroxide adsorbed. Here again there is great difference of opinion. Many physicians disapprove of alum precipitated vaccines on account of violent reactions and abscess formation. Lapin⁷ is against them, claiming that "The low pH. of alum vaccine seems to summate the necrotizing power of *Hemophilus pertussis* so that 25 per cent or so produce severe reactions and 5 per cent produce abscesses." Sako⁹ on the other hand strongly favors the use of alum. He had 3.3 per cent abscess formation in his series. He believes deep injections are followed by fewer abscesses, and that the leakage of the vaccine into the subcutaneous tissue was what gave rise to them. He advises using a separate needle to withdraw the vaccine from the vial, replacing it with a fresh needle after drawing up the required amount into the syringe. By this procedure the outside of the needle would be free from vaccine. Since using this technique, over 1000 injections have been given without a single abscess.

Personally I have preferred fluid solution and am inclined to agree with Geoffrey Edsall¹² whose excellent review of active immunizations appeared in August 1946 in the New England Journal of Medicine. I would advise all who are interested, to read this. He advocates plain vaccine given alone in early infancy.

This brings us to the question of the simultaneous use of several antigens. Some years ago Ramon showed that a number of antigens could be mixed and injected together. Almost everyone now admits that tetanus and diphtheria toxoids may be given together, but there are many who doubt the advisability of adding pertussis vaccine. I have had

some very severe reactions when all three antigens were simultaneously injected and again would, for the present at least, follow the scheme proposed by Edsall where pertussis is given alone at 3, 4 and 5 months, followed by the combined diphtheria and tetanus at monthly intervals after that. It is true that this schedule necessitates six injections which do not necessarily improve the infant's morale. The baby is brought to the pediatrician at monthly intervals for the first nine months of life, so the number of visits is not increased by the schedule and I believe there will be fewer reactions. I have been using only plain vaccine and plain toxoid and have had very few reactions and no abscesses whatever.

When it comes to the proper dosage of pertussis vaccine, we are again confronted by great differences of opinion. You may remember that when Sauer¹³ first introduced his method, he advocated a total dose of 40 billion organisms. Since that time the dosage has been steadily increased, so that some authorities, including Lapin, advocate 120-140 billion. He showed that in a 3-year period, the communicability rate of 200 infants inoculated with 120 billion was only 9.6 per cent compared with an average of 31-39 per cent for those given 80 billion in a previous 3-year period. He found no difference in three groups of infants, as regards pain, induration or febrile reaction, who were given vaccine in the following concentrations: Group I, 40 billion per cc., 1 cc. 3 times; Group II, 15 billion per cc., 2 cc., 2 cc. and 4 cc. (2 cc. in each arm); Group III, 20 billion per cc., 2 cc. 3 times. According to these results 1 cc. of vaccine containing 40 billion bacilli per cc., given three times at monthly intervals should be the best procedure. Monthly intervals have been shown to be preferable to the weekly intervals first used, as the immunization titer is definitely greater when the injections are given at longer intervals.

In San Francisco, Miller¹⁴ and a group of investigators highly favor the use of combined tetanus and diphtheria toxoids (aluminum adsorbed) to which pertussis vaccine has been added. They prefer two injections of 1 cc. each at 12-week intervals. Only 20 billion pertussis organisms were given per cc., and the results for immunity to pertussis were not satisfactory wherefore another (third) injection of pertussis alone was given. This would mean three injections in all. They had no abscesses in 344 injections. Whether aluminum adsorbed toxoid with added pertussis vaccine is to be the method of choice remains to be

seen. You will remember that according to Sauer, Lapin and others, the dose of pertussis vaccine is not nearly large enough. Only time will tell which is the ideal method. All authors are agreed that it is now possible to immunize from 75-90 per cent of infants injected.

In September 1947 Di Sant' Agnese¹⁵ of the Babies Hospital in this city reported the results of a large series of prophylactic injections of combined diphtheria, tetanus and pertussis in infants ranging in age from three months to two years. The great majority of the children were between the ages of 6 and 12 months, but the series included 30 between the ages of 3 and 5 months. He used two preparations: (1) Fluid diphtheria and tetanus toxoid containing 40 billion H. pertussis per cc. and -(2) aluminum hydroxide adsorbed tetanus and diphtheria toxoids, with 20 billion ($\frac{1}{2}$ the above) H. pertussis per cc. He ran two parallel series, giving three injections, one month apart—0.5, 1.0 and 1.0 cc. I should like to quote some of his conclusions: "In 635 injections of the two immunizing agents, it was found that the systemic and local reactions to the two preparations did not differ significantly. It was noted that the type and the intensity of the local reactions did not depend on the size of the injection, but decreased with subsequent inoculations. Constitutional reactions were not severe and no sterile abscesses requiring drainage were observed.

"The post-immunization titres were satisfactory in both series of cases. It was felt that alhydrox was a better immunizing agent against pertussis than plain D.P.T. vaccine because equally good results were obtained with half the dose of H. pertussis. In the case of diphtheria and tetanus, alhydrox was also found to give better results. The anti-toxin titres obtained with this agent were higher and more enduring than those obtained after the injection of the plain D.P.T. vaccine."

From these various reports you will realize that as yet there is no unanimity of opinion as to the best method of giving infants prophylactic injections. However, I think one may advise immunization at an early age especially against pertussis and may recommend the aluminum hydroxide adsorbed preparation as the best if protection against diphtheria, tetanus and pertussis are to be given simultaneously.

I should also mention that attempts to protect the very young infant have been made by injecting the pregnant mother with vaccine. Kendrick et al¹⁶ showed that there was strong evidence of placental transfer of antibodies. Cohen and Scadron¹⁷ also advise the inoculation of the

mother during the last trimester of pregnancy, their special point being that the mother of today has less immunity to pertussis and that as a result, the new born infants have little or no resistance to the disease. It should be remembered that immunity acquired from the mother is weak and does not last long.

Mention should here be made of the fact that occasionally in whooping cough the etiological agent is not *H. pertussis* but the parapertussis organism. This often accounts for so-called second attacks of whooping cough. Quite recently Rambar and his co-workers¹⁸ have reported a series of infants protected by a vaccine made up of *H. pertussis* and *B. parapertussis*. They obtained evidence of a high level of immunity against both organisms and suggest the addition of parapertussis organisms to the pertussis vaccine used for routine immunization.

Now as to the treatment of whooping cough, we have one new weapon, namely hyperimmune serum, which is a very valuable addition to our armamentarium. The serum may be made by injecting rabbits or human volunteers with *H. pertussis* until a very potent antiserum is produced. For a time this could only be obtained from the Philadelphia Serum Exchange. The human serum is obviously preferable. The product is furnished in solution or as a lyophilized powder. When reconstituted, about 20 cc. must be injected 1-4 times. Obviously, the large bulk is a great disadvantage but I have seen remarkably good results with it. I treated a premature infant whose mother had a cough not recognized as pertussis till the baby was a week old. Two weeks later the infant developed typical whooping cough. It received three injections of hyperimmune serum and recovered. With the advent of the discovery of the fractionization of serum by Edward Cohn,¹⁹ it was natural that the gamma globulin fraction should be examined for its ability to carry pertussis antibodies. It has been found that by the use of gamma globulin of hyperimmunized individuals, the strength of the dose may be concentrated twenty-fold so that now an injection of 1 or 2 cc. only is required. This product is expensive and at times hard to get but it is the drug of choice both for passive immunization of contacts and for treatment especially of infants.

Jerome Kohn and Alfred Fischer²⁰ recently emphasized the great advances that have been made in handling pertussis in infants. The mortality at Willard Parker Hospital has been reduced in infants under one year by the use of the following: 1) hyperimmune serum, 2) oxygen,

3) chemotherapy, 4) suction, 5) extremely good nursing care, 6) antibiotics. Since much of the damage, especially in young infants, caused by anoxia is due to the accumulation of viscid secretions in the respiratory passages, the use of oxygen and suction are of really great importance. Physicians who may have to treat pertussis in infants at home may now avail themselves of the small plastic oxygen tents in which the oxygen concentration may easily be kept at 50 per cent. Electrically operated suction devices, using a #12 catheter with multiple stomata may be kept at the bedside. Careful nursing and the prevention of anoxia are of the greatest help in reducing mortality.

Statistics on the use of hyperimmune serum and globulin have also quite recently been published by Kohn²¹ and his associates at Willard Parker Hospital. They conclude that its use shortens the period of severe paroxysms and lessens emesis. They recommend its use in all infants who are seriously ill with whooping cough. Their mortality rate in seventy-nine infants under one year of age was only 1.2 per cent.

To conclude our review of pertussis we may say that we have made advances both in its prophylaxis and treatment and that if we recognize the disease early and apply the most recently advocated methods of therapy, we stand a very good chance of obtaining a cure even in very young infants, whereas, not so long ago, the outlook for the recovery was very dubious.

MUMPS

Until quite recently the average physician has looked upon mumps as a rather uninteresting disease which most persons acquire in early life, the disease being characterized by swelling and tenderness of the salivary glands, occasionally complicated by orchitis or meningoencephalitis. During the past few years, however, many interesting investigations have given us a much more comprehensive idea of mumps and have placed at our disposal several diagnostic procedures of great value. In 1934 Johnson and Goodpasture²² demonstrated conclusively that mumps could be transferred to the Rhesus monkey by the inoculation into the parotid, of saliva from patients ill with the disease. The difficulty of having to use the monkey as the only means of growing the virus naturally handicapped investigators until 1945 when Enders and also Habel succeeded in growing the virus in the developing hen's egg. By this method the virus has been kept growing by passage through

many eggs and as a result, inexpensive material is available in sufficient amount to carry on studies and to use in diagnostic tests.

The two most important results of this work are the discovery of the complement fixation and the skin tests for mumps. Since complement-fixing antibodies are found in diseases of viral origin, they were looked for here too and it was found that they were present with such regularity that they might be used as a diagnostic test. Enders²³ has reported on his findings in numerous publications and has shown that a few days after the onset of mumps, the antibody titer in the circulating blood begins to rise and that as convalescence proceeds very high titers are reached. He used an emulsion of the parotid glands of infected monkeys as antigen and could very definitely prove the regular appearance of increasing antibody titer as the disease progressed. Since it was not only the exact titer that was desired but the relation of the titers early and late in the disease, it became necessary to obtain two specimens of the patient's blood; one early in the illness, the other after 2-3 weeks. The great increase in antibody content definitely stamps the disease as mumps.

With the complement-fixation test as a guide, it has become possible to diagnose mumps in the absence of salivary gland swelling. As you know, one of the common complications of mumps is meningoencephalitis. This usually makes its appearance a few days after the appearance of parotid swelling. It is characterized by signs and symptoms of meningeal irritation and may simulate several other diseases such as poliomyelitis, choriolymphomeningitis, equine encephalitis, etc. All these diseases are characterized by fever, headache, vomiting, irritability or lethargy and at times somnolence or coma. Lumbar puncture reveals pleocytosis with increase in the lymphocytes in the spinal fluid. By the use of the complement-fixation test, it is now possible to diagnose encephalitis due to mumps and to separate it from the encephalitis of other etiology. Let me give you an example: A.B. aged 10 was a boy whom I saw in the fall of 1945. He lived in a neighboring town where there had been considerable poliomyelitis during that summer. On Sunday he complained of a severe headache, vomited and became drowsy. I was asked to see him the following day. He was dull and lethargic, had fever up to 103 and a slow pulse. He had marked rigidity of the neck, bilateral Kernig's sign and diminished reflexes. There were no paralyses to be elicited. He swallowed well. The eyes and fundi were negative.

A diagnosis of polioencephalitis had been made. On going into the history it was ascertained that this lad and two friends were in the habit of going to the movies every Sunday. Six weeks before the onset of this illness one of these boys had come down with parotid mumps. Three weeks later the second boy had the same symptoms. Now again just 21 days later, my patient developed signs of encephalitis. As a result of this history, the case was diagnosed as mumps. Blood was obtained for complement-fixation and sent to Boston. A lumbar puncture revealed 400 cells, all lymphocytes. Pandy test was positive. The blood revealed 7200 white cells, with 33 per cent polymorphonuclear cells. The boy was carefully observed, but at no time in the course of the illness were there signs of parotitis or orchitis. The temperature fell rapidly and in a few days the boy was convalescing. Blood taken 14 days later showed a great rise in the titer of complement-fixing antibodies, proving that the boy was suffering from mumps.

If a case such as this is kept in mind, you will come across similar instances of mumps apparently limited to the meninges. In this connection I would like to stress a point emphasized by Dr. Janeway of Boston, namely, the importance of careful, frequent examination of the salivary glands and in boys of the testes in every case of encephalitis. It is of great interest to note that parotitis or orchitis may be observable only for a very short period and then only in a very mild degree. If the case of encephalitis of questionable origin is in a hospital, the internes should be made aware of this fact and should be instructed to look for parotid or testicular signs several times a day. The finding of a fleeting swollen parotid or a tender testis in the course of encephalitis is enough to stamp the case as one of mumps.

Mumps may also set in with severe headache, high fever and vomiting, so that a cerebral condition is suspected. After a period varying from a few hours to a day, typical parotid swelling appears and the case continues as one of ordinary mumps. Although there are frequently no definite meningeal signs, it is probable that all these cases have a mild meningoencephalitis.

Another interesting complication of mumps, to which attention has been recently called is involvement of the myocardium. Rosenberg²⁴ has reported two isolated cases with heart block in the second week of the disease. In a study of 104 consecutive cases of mumps in adults, electrocardiographic evidence of myocardial involvement was found

in 16 (15.4 per cent). It occurred usually between the 5th and 10th days, was mild and transitory and was subclinical.

I was asked to see a young man of 27 whose father, a cardiologist was much upset because the onset of an acute illness with headache and high fever, which turned out to be mumps meningoencephalitis, was accompanied by such dyspnea on exertion that the boy had great difficulty in climbing two flights of stairs to his bedroom. The electrocardiogram showed a slight change but not enough to justify the diagnosis of myocarditis.

Now a few words as to the skin test for mumps. This had been elaborated by Enders,²⁵ and Stokes²⁶ and their collaborators and I quote the following conclusions from one of their publications:

"1. Persons exhibiting erythematous dermal reactions exceeding 10 mm. in mean diameter 48 hours after the inoculation of a suspension of heated, inactivated mumps virus obtained from the parotid gland of infected rhesus monkeys may be, from the practical standpoint, regarded as resistant to mumps. According to this criterion, an error in interpretation of about 10 per cent may be made. This error will be reduced to approximately 2 per cent if a reaction larger than 15 mm. be taken as the criterion for the resistant state.

"2. Preliminary tests employing skin test material prepared from the amniotic membranes of infected chick embryos show that it also exhibits the capacity to induce local reactions in individuals hypersensitive to the virus or its products.

"3. In general the attack rate of mumps in exposed groups will be low when the incidence of positive skin reactors exceeds 50 per cent. The skin test might, therefore, be employed to obtain an estimate of impending morbidity in family groups or units of institutionalized or military personnel.

"4. By means of the skin test, additional evidence has been obtained which indicates that subclinical attacks by the virus of mumps are frequent, accounting in young adults for about 33 per cent of past infections.

"5. The skin test in adults is in most instances a more sensitive indicator of past infection and hence of immunity than is the complement-fixation test.

"6. The skin test material is antigenic, giving rise to the formation or increase of specific complement-fixing antibody.

"7. It is possible, though not demonstrated, that skin testing may lead to increased resistance to infection by the virus.

"8. From a comparison of certain general epidemiologic features of mumps with those of other diseases in which the phenomenon of 'population immunity' is already established, the findings reported here are in accord with epidemiologic expectancy."

It was natural that attempts at prophylaxis and treatment of mumps should be carried out, now that we can obtain sufficient amounts of the virus. Convalescent serum has been used and in some instances has been reported to be helpful. Rambar²⁷ in a recent publication concluded that the occurrence of complications was reduced when 40 cc. of convalescent mumps serum was injected at the onset of the illness. However, Enders, Stokes and their collaborators obtained different results. They showed that in the gamma globulin prepared by Cohn, from pooled normal adult plasma, the mumps complement-fixing antibody was concentrated 15 to 25 times. They showed that in spite of this, the globulin did not protect when injected, as it does in measles. Large amounts of this material were injected by others (Gillis, McGinness and Peters) early in the disease without reducing the frequency of the occurrence of orchitis. They did find, however, that when the gamma globulin was prepared from convalescent mumps serum and 20 cc. was injected, the occurrence of orchitis was greatly reduced. It is of interest to note that this 20 cc. is equal to about 400 cc. of convalescent serum or 200 cc. of normal gamma globulin. They further report work in which virus, partially inactivated by repeated egg passage, has been used as prophylactic with very promising results.

To conclude then we may say that we have a complement-fixation test and a skin test for mumps and that we are making definite progress toward the discovery of prophylactic and therapeutic injections for this disease.

RUBELLA

Of all the recent developments in the study of contagious disease, none is more dramatic and exciting than the discovery of fetal defects due to rubella in the pregnant mother. Until 1941 rubella was considered a mild, harmless illness which rarely resulted in complications or sequelae. However, in that year an Australian ophthalmologist, Gregg,²⁸ reported a remarkable series of congenital cataracts. He observed 78

cases of congenital cataract in infants born in the neighborhood of Sydney between December 1939 and January 1941. He noted that the mothers of all of these infants had suffered from rubella in the early months of their pregnancies. He wrote, "The most striking factor is that the cataracts, usually bilateral, were obvious from birth as dense, white opacities occupying the pupillary area. Most of the babies were of small size, ill-nourished and difficult to feed, with the result that many of them came under the care of the pediatrician before being seen by the ophthalmic surgeon. Many of them were found to be suffering from a congenital defect of the heart."

The following questions at once arose: (1) Was the disease affecting the mother really rubella? (2) At what period of pregnancy did the disease affect the offspring? (3) Did the disease cause fetal defects other than cataract and heart disease and (4) Did such fetal defects follow other maternal infections? From careful studies by Gregg, Swan and others²⁹ in Australia, it appears that the disease in question was rubella. It caused fetal damage especially when the mother acquired the disease in the first three months of pregnancy. According to the data collected in Australia, if the disease occurred in the first six weeks of pregnancy, almost 100 per cent of the offspring were affected. A few cases were reported where the disease occurred after the first trimester. Besides cataract and heart disease, the following pathological conditions were encountered: deaf mutism, mental retardation, glaucoma, microcephaly and hypospadias.

Since these reports which appeared in the Australian literature in 1941, 43 and 44, many cases have been encountered in the United States. Last year I was able to collect over 200 cases. I personally have seen six cases, all of them having ocular lesions, five cataracts and one glaucoma. The children were all mentally retarded. One was of interest because the child had a congenital cardiac defect, bilateral cataracts and deaf mutism. Since the birth of this child, the mother has had two normal children.

Statistics are quite conclusive that the earlier in pregnancy the mother comes down with rubella, the more certain it is that the infant will be affected. There are some recorded instances where infection took place as late as the seventh month with resulting fetal malformation. We need more knowledge concerning the occurrence of maternal rubella without fetal disease. I have seen one such case where the

mother contracted rubella in the fourth month of pregnancy and gave birth to a perfectly normal infant.

A review of the literature fails to show similar defects following other contagious diseases except for one case of mumps and one of influenza.

The effect of rubella on the fetus is of great interest in the study of congenital malformations for it proves that the latter may and do arise as the result of a toxin affecting the already fertilized and developing ovum. It has been pointed out that young, undifferentiated tissue is particularly vulnerable to virus infection and this is borne out by the fact that the earlier in pregnancy the mother develops rubella, the more surely will the fetus be affected.

From our knowledge of this new entity, I think we should try to expose female children to rubella wherever possible, so as to attempt to immunize them. During an epidemic of rubella, women in the early months of pregnancy should be warned to avoid exposure. So far, we have no protecting serum. In one instance gammaglobulin was injected into the mother after she had the illness, but the resulting infant had defects.

Termination of pregnancy in women who develop rubella during the first few weeks of gestation brings up many complex questions. In New York State it is illegal to perform abortion unless the health of the mother is in question. Absolute advice cannot be given until we know the actual percentage of affected infants. We have as yet scarcely any data on the frequency of normal offspring after maternal rubella. If it should be found that this is a very infrequent occurrence, physicians will probably want to have pregnancies terminated.

MEASLES

Turning to measles, we can here also record brilliant advances during the past few years. The value of convalescent serum both as a therapeutic and a prophylactic agent is well known to all of you. Whole adult blood was first used, later the blood serum was employed since a greater amount of protective substances can be given in the same bulk to be injected. Then you will recall that in order to obtain more material, the human placenta was used and we had a product named Placental Extract. The theory upon which this therapy was based depended on the fact that almost all adults have at one time had measles

and that their blood contained antibodies. By the injection of adult serum, these antibodies were carried into the child and acted as passive immunizing substances. We were all pretty well satisfied with convalescent serum, but it was necessary to use a rather bulky injection. It was therefore a great step in advance when Edwin Cohn at Harvard devised a simple method of fractionating human plasma. The antibodies which carry the immunizing substances are found to be present in the globulin fraction, especially in the gamma globulins. It was shown that the antibody content and therefore the therapeutic potency was concentrated twenty-five times in the process of fractionization. Thus 1 cc. of gamma globulin has the same therapeutic value as 25 cc. of plasma, and its value to us is due to this fact, for with a very small injection we can accomplish the same effect as we previously did with a large one. Moreover, gamma globulin rarely gives rise to unpleasant reactions.

The work of Cohn, Enders,³⁰ Janeway,³¹ Stokes and others has definitely shown that gamma globulin is the best prophylactic agent for measles. Depending on the dose we give, we may either attenuate the disease and get so-called Modified Measles, or by increasing the dose we may prevent the disease altogether. Since, if we prevent the disease, the immunity lasts only a few weeks, it would seem wiser to attempt to produce modification of the disease so that the child with a very mild illness might obtain permanent immunity. The difficulty of obtaining globulin for employment in practice is such, that its use must be somewhat curtailed. The ideal situation would be to give every exposed child a dose of globulin. Children already ill with other diseases, very small infants, tuberculous children, gravid mothers in their first months of pregnancy, children exposed in hospital wards should receive large enough doses to protect them completely. All others should be permitted to have the modified form of the disease.

The dose for modification is 0.02 cc. per pound. The dose for prevention is 0.1 cc. per pound. I want to make clear the point that in the preparation of gamma globulin for use against measles, pooled adult blood is used because we know that almost every adult has had measles and that his blood contains antibodies. This is not the case with other illnesses. For example, the same gamma globulin used for measles is found to be ineffective for mumps. However, if gamma globulin is prepared from mumps convalescent serum, a potent agent is obtained. In the same way volunteers have been injected with pertussis bacilli

until their blood showed a very high immune titer, after which their gamma globulin has been precipitated giving us an extremely concentrated potent product.

With the intelligent use of globulin and the added advantage of the availability of sulfa and penicillin to treat complications, measles has been robbed of many of its terrors.

I believe that from this brief review you will agree with me that in recent years we have made great strides in our knowledge of the contagious diseases of childhood and that progress has not only led to a better understanding of these diseases but has enabled us to make practical use of many new methods, in diagnosis and especially in therapy so that we are now able to approach their treatment with real confidence and assurance.

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THE DEVELOPMENT OF HYDROTHERAPY*

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THE water cure is one of the most ancient therapeutic measures and one which has enjoyed the widest popularity, aside from outright magic or other psychotherapeutic measures relying for their efficacy exclusively on suggestion. The earliest and also some of the more modern hydrotherapeutic techniques in many of their applications have partaken of the character of sympathetic magic and psychotherapy. Examples are the sacred springs of Vishnu in India, the fountain of Arethusa in Greece and the Jordan River in Palestine, all waters which were once or are still today believed to cleanse the faithful not only of filth but also of sin and disease. On the other hand, the success of many spas and watering places in their competition with centers of religious healing indicates that for certain conditions the water cure was often deemed more agreeable or more effective.

In its application to both business and pleasure balneology was developed to an unparalleled degree in the declining centuries of the Roman Empire. From the earlier civilizations about the Mediterranean area virtually no remnants of plumbing facilities are extant except in the royal palace at Knossus in Crete. The Romans employed armies of captured slaves to assemble stone aqueducts, such as the Claudian, to supply their bath-houses. The baths themselves were massive architectural undertakings of which those of the Emperors Diocletian and Caracalla were notable examples and served as forerunners of such modern structures as the Grand Central Station in New York. It is not known precisely how the Romans took the waters. From the remains of baths, of which those at Pompeii are well preserved, it has been postulated that the bathers progressed through successively hotter *tepidaria* and *caldaria*, finally to loll in a steam room in which they

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were massaged and then scraped with a *strigil* before plunging into a pool in the *frigidarium*.

After centuries of conflict with the barbarians and corruption from within, the Roman Imperial governments became too feeble to maintain large scale public enterprise; the aqueducts were cut by the Huns and the baths became rock quarries. Far from being forgotten, however, the delights of these ancient thermae were revived and even exceeded in refinement, if not in size, by the Saracen merchants and princes of the medieval Byzantine Empire at the Eastern end of the Mediterranean.

In the Europe of the Middle Ages and the Crusades bathing fell into widespread disrepute and was denounced as a gratification of the flesh. Bath houses functioned more as bawdy houses than as centers of sanitation or good clean fun. In the Italian language the application of the term *bagnio* to such institutions has persisted to the present day. Indeed the excesses of the patrons of the Roman baths recorded in the writings of Petronius and Suetonius appear to have been equaled or exceeded in the smaller medieval public baths of which those at Bruges in Belgium and Baiae in Italy may be taken as examples.¹

Despite the prevailing dissociation between cleanliness and godliness, which kept many of the holiest personages of the Moyen Age bathless for life and provided a fertile ground for the spread of epidemic and pandemic louse-borne diseases, there survived in many localities the primitive tradition of employing the bath in a therapeutic role, and a profound faith in the curative powers of the waters. Indeed the repute of most of the world famous spas, for example, those at Bath in England, at Poitiers in France, at Monte Falcone in Italy, Baden Baden in Germany, and Budapest in Hungary, date back to early medieval times.

An evaluation of the importance of the water cure and spa therapy in general in medieval medicine may be made from the numerous medical texts on this subject which appeared following the introduction of printing. These early treatises were devoted in the main to earnest but tedious scholastic commentaries on the teachings of Hippocrates and Galen relating to the spas and to the various forms of hydrotherapy. Elaborate rituals were pursued. The well-known mechanical ingenuity of the Swiss is revealed in a remarkable hydrotherapeutic installation which was apparently in operation in the latter part of the 15th Cen-

tury. In the fever of the search for new cures virtually every spring and rivulet on the continent of Europe was tested for therapeutic properties. One Spanish adventurer, Ponce de Leon, wandered even to the coast of Florida in the pursuit of a fountain which would preserve everlasting youth.

In modern times a survival of some of the ancient methods of hydrotherapy is seen in the sweat baths of the Gaels, the Finns, and the Russians, paralleling a custom of the North American Indians. In a small enclosed hut, clouds of steam are evolved by pouring water on hot stones. This heated vapor initiates a sweat which may be followed by a cold plunge or a roll in the snow. Similar in effect are the steam rooms of the Turks and the Romans. The Japanese have resorted for centuries to courses of almost intolerably hot baths in plain or mineral-bearing springs of Japan. A course of treatment in some of the hot sulfur-bearing springs of Japan causes an eczematoid dermatitis which is regarded as a necessary preliminary to the cure.²

The 18th and 19th Centuries brought the spas of Europe to new heights of popularity and prosperity. Hundreds of books and papers were written to advertise the virtues of this or that spa or a new method of hydrotherapy.

One Kneipp, a Bavarian monk of the early 18th Century, accumulated a large following and many imitators by the simple expedient of dousing his patients with ice water. Kneipp ultimately fell into disgrace after being invited to try his own treatment on an aged and decrepit Pope. Priessnitz, an Austrian peasant of the same period, made a remarkable recovery from multiple contusions and fractures by dousing himself and gulping down large quantities of water. Attributing this dramatic cure to the effects of the temperature of water used, he set about to confirm or disprove his impression by a scientific experiment involving the feeding of one small pig on hot foods and another on cold foods. At the time of slaughter, the test animal fed upon cold food had firm well contracted intestines while the animal fed upon hot food had such red and friable viscera that it was useless for sausages. Priessnitz' alleged contribution to therapeutics was the popularization of his methods of inducing sweats and chills by his cold wet applications.³

For the most part the expanding literature on hydrotherapy of the 18th and 19th Century was European in origin. American therapeutic spas never achieved any great practical importance and the number of

such institutions has declined.⁴ The apathy to this modality of treatment in America appears perhaps to stem not from the fact that the public is any less hypochondriacal or the profession less credulous with respect to claims for 'mineralized' or 'radio-active' waters such as those at the famous springs of Europe, but more from the fact that the American spas have not been effectively advertised and promoted. The courts of last appeal for the sick in the United States and Canada have been the public or voluntary hospitals instead of the spas; the fashionable watering places serve more exclusively as recreation centers.

Thus in the United States it has been mainly by the unremitting efforts of one single minded enthusiast, Dr. Simon Baruch, that certain of our best hydrotherapeutic procedures have come into general use, notably the all-important wet pack or tepid bath for the control of disturbed psychotic patients, the alcohol or sponge bath for the relief of fever and the public bath houses of the City of New York.^{5,6}

Hydrotherapy and manipulative techniques have fallen into a state of disrepute in the hands of the cultists yet the disregard of many physicians for the practical value of these techniques in the management of certain chronic diseases has frequently resulted in unnecessarily poor therapeutic results. The proper application of hydrotherapy and manipulation for patients with chronic arthritis and for the rehabilitation of patients with vascular or nerve and muscle injuries exceeds in value many of the prevailing current practices in the treatment of these conditions.

There has been a notable revival of interest in the development of effective methods for rehabilitation and proper management of chronic disease and old injuries, a movement dating approximately from the time of the first World War.⁷ Large and small therapeutic pools have been installed and utilized with gratifying results in an increasing proportion of the major hospitals of the United States.⁸ A brilliant application of hydrotherapeutic techniques is exemplified in the bold departure of the Sister Kenny method from some of the older orthopedic measures applied to the management of acute and convalescent stages of poliomyelitis. Further progress has been made in the application of hydrotherapy to the hospital practice of medicine by Hubbard's introduction of a block T shaped tank for underwater exercise in poliomyelitis cases.

The Currence tank was first designed and installed at the New

York Post-Graduate Hospital in 1935. It was originally intended only for underwater rehabilitation of osteoarthritic patients. Its shape is such that the technician has ready access to the patient's body and extremities. It has thermostatically controlled water temperature, two turbines adjustable on a track for hydromassage and an overhead crane to simplify the handling of helpless patients.⁹ This tank has widened the availability of general hydrotherapy inasmuch as it has been installed in hospitals throughout the country. Although this tank was originally designed only for treatment of osteoarthritis its flexibility of usage has greatly widened its scope. It is now used to induce low grade hyperexia,¹⁰ to restore muscle tone following debilitating febrile and cardiac illnesses where exercise is desirable with a minimum expenditure of effort for the patient. In fibrosis and fibrositic ankylosis of shoulders, hips and knees, in Marie Strumpel's disease, curvature of the spine, many cases of chronic low back pain, numerous neurological conditions and following many orthopedic operations and manipulations, it is useful.

Cases of surgically pinned fractures of the neck of the femur start underwater exercise as soon as the wound is healed, usually by the tenth day. Probably one of the most gratifying observations is in cases of hemiplegia following cerebral hemorrhage where rehabilitation exercises are started as early as the seventh day.

Summary: Although hydrotherapy is one of the oldest remedial agents known it was formerly available only to those who were able to travel to institutions usually located where there were natural springs. Until recent years, its use has been on an empiric basis, often named the "Cure," and consisting of twenty-one daily baths identical in nature regardless of the diagnosis and probably often without diagnosis.

At the present time the benefits of hydrotherapy can be provided in any hospital. Modern hydrotherapy is now prescribed by dosage in type, time and temperature with anticipated physiologic effect to cope with individual requirements just as other therapy is prescribed.

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IN MEMORIAM

DR. JAMES ALEXANDER MILLER

TRIBUTE BY THE COUNCIL

THE COUNCIL of The New York Academy of Medicine records with deep feeling its sense of loss in the death on July 29, 1948, of Dr. James Alexander Miller.

Few men in the history of the Academy have so deeply left the impress of their spirits, personalities, and abilities as did Dr. Miller. A Fellow for forty-four years, a member of the Committee on Public Health Relations for thirty-five years and its Chairman for fifteen years, for seventeen years a Trustee, and for two years President of the Academy, and finally in the Centennial year the recipient of the Academy Medal, awarded to him for outstanding services to the Academy and to humanity—all of this only suggests the vast contribution which Dr. Miller made to the life, growth, and progress of this institution.

Endowed with a mind, judicial, searching and clear, it is difficult to overestimate the part he played in shaping the policies and course of the Academy by his sound counsel and great understanding. To a great degree, the prestige and influence of the Committee on Public Health Relations under the guidance of Dr. Miller, have been a reflection of his own broad interests on behalf of the health and welfare of the community. Eminent in the field of clinical medicine, effective as a teacher and as an organizer, loved and respected by his confreres, his patients and his friends, all he was and all he did redounded to the glory of this Academy which he both served and led with such loyal devotion for so long a period.

Mindful of the great loss sustained by The New York Academy of Medicine in the death of Dr. Miller, the Council orders that this resolution be spread on its minutes and that a copy thereof be presented to his family.

October 27, 1948

TRIBUTE BY THE COMMITTEE ON PUBLIC HEALTH RELATIONS

D R. MILLER was one of the founders of the Committee on Public Health Relations which was organized on May 1, 1911. Although at the time he was one of the youngest, if not the youngest member of the Committee, he very soon became its directing genius. More than any other single person, he helped to establish the Committee's course of action and to mould its policies. His keen mind and clear vision, his tact, dignity and judicial temperament, his high sense of reality and his statesmanlike progressive attitude toward community requirements made him a peerless leader.

He became Chairman of the Committee in 1929, having acted temporarily in that capacity on many occasions during his predecessor's illness. In 1936, upon election to the presidency of the Academy, Dr. Miller resigned the chairmanship of the Committee but was persuaded to accept it again in 1942 during the war when the then Chairman joined the armed forces. Although suffering a great deal of physical pain during the last few years of his chairmanship, he kept a devoted interest in the work of the Committee, and except for the last year, attended meetings regularly, though with much effort.

During his continuous service on the Committee for thirty-seven years, Dr. Miller exercised great influence on public opinion, on methods of procedure in public health and allied fields, and on the attitude of the medical profession toward many of the complicated problems that lie between clinical medicine and medical education on the one hand, and community needs on the other. In the course of his long public activity, he gained many devoted friends and followers, and he has left an indelible imprint on the annals of his time.

The Committee herewith wishes to record with deep emotion its profound sorrow in the passing of its beloved leader, a great physician, a great humanitarian, and a great educator.

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